APASL STC 2023 BUSAN

The Korean Association for the Study of the Liver

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

Scientific Program

DAY 1 | Thursday, Sept. 21, 2023

ROOM 1

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DAY 3 | Saturday, Sept. 23, 2023

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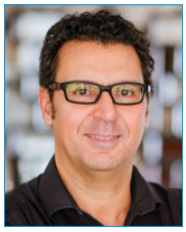
Invited Faculty List

"Special Thanks to the Invited Faculty"

We appreciate your time and efforts during the conference. Together, we will move towards eliminating viral hepatitis.



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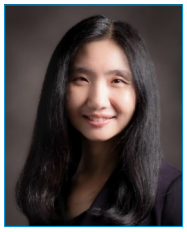

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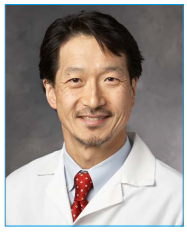

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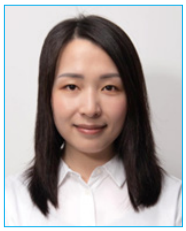

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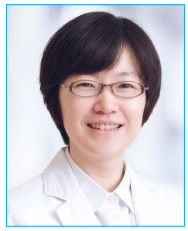

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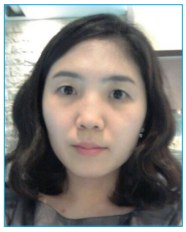

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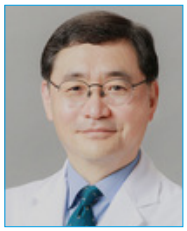

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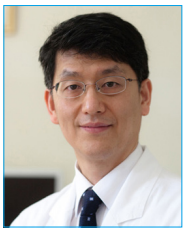

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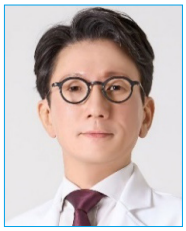

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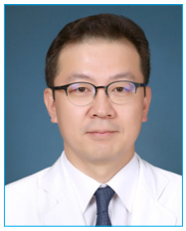

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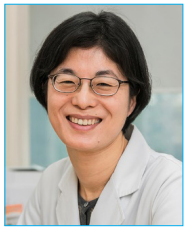

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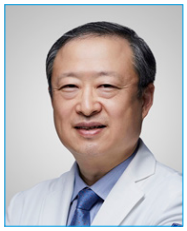

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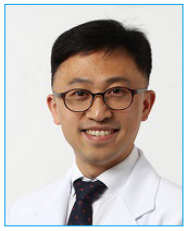

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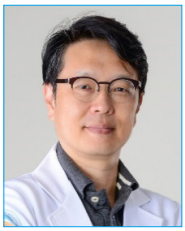

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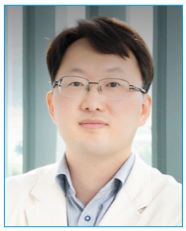

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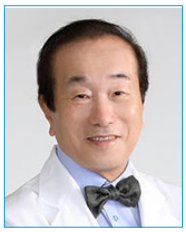

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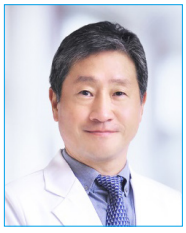

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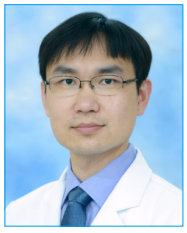

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APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 1 | Thursday, Sept. 21, 2023

Pre-Congress Symposium

Chairs:

Byung Ik Kim (Sungkyunkwan Univ., Korea)
Young Oh Kweon (Kyungpook National Univ., Korea)
Youn-Jae Lee (Inje Univ., Korea)

Updates on Epidemiology and Natural Course of Viral Hepatitis in Asian-Pacific Region: HBV

Jeong Eun Song

Daegu Catholic Univ., Korea

Globally, HBV infection is a serious public health problem owing to its high prevalence and the high probability of progression to cirrhosis and hepatocellular carcinoma (HCC). Approximately 296 million people, or about 3.8% of the world's population, are chronically infected with HBV.[1] The prevalence of HBV infection is highly heterogeneous throughout the world, with an intermediate to high prevalence in the Asian-Pacific region, representing three-quarters of chronic HBV infection worldwide.[2]

Prior to implementation of the HBV vaccination program, the Asian-Pacific region was divided into three categories in terms of HBsAg prevalence.[3] High-prevalence (>8 %) regions included mainland China, Hong Kong, Taiwan, South Korea, Mongolia, Philippines, Thailand, Vietnam, and the South Pacific Island nations. Intermediate-prevalence (2-8 %) regions included central Asia, the Indian subcontinent, Indonesia, Malaysia, and Singapore. Low-prevalence (<2 %) regions included Australia and New Zealand.

Owing to universal HBV vaccination at birth in past three decades has dramatically changed the epidemiology of chronic HBV infection. A systematic review published by WHO experts in 2012 showed a decrease in prevalence of chronic HBV infection from 1990 to 2005 in most Asian-Pacific regions.[4] In China, HBsAg seroprevalences in the population aged 1-59 years decreased for 9.8% in 1992 to 7.2% in 2006.[5,6] In Taiwan, HBsAg seroprevalence decreased tenfold from 1984 to 2009.[7,8] In South Korea, HBsAg seroprevalence has decreased from 4.61% in 1998 to 2.90% in 2013.[9,10] In Thailand, the prevalence of HBsAg was reported as 4.0% in 2004 and 2.2% in 2014.[11-13] Lihn-Vi et al measured the progress in Asia and Pacific in achieving key impact targets for 2020 by modelling disease burden and the cascade of care.[14] Between 2015 and 2020, chronic HBV prevalence has decreased from 4.69% to 4.30%. Among 5-year-old children, HBV prevalence fluctuated as a result of large vaccination coverage fluctuations in key countries but decreased by 30% between 2015 and 2020. Although chronic HBV prevalence declined between 2015 and 2020, the incidence of HCC related to HBV infections still increased by 9% and liver-related deaths from HBV rose by 8%. It is worrisome that only 13% of chronic HBV infections were diagnosed and 25% treated.

The Asian-Pacific region had made substantial progress in reducing HBV incidence and prevalence. This was largely due to universal infant vaccination against HBV beginning in the late 1990s in many countries in this regions.

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Updates on Epidemiology and Natural Course of Viral Hepatitis in Asian-Pacific Region: HCV

Nae-Yun Heo

Inje Univ., Korea

Hepatitis C virus (HCV) is one of the major causes of chronic viral hepatitis, second only to the hepatitis B virus. Chronic HCV infection can progress to cirrhosis and hepatocellular carcinoma, which have catastrophic consequences. According to the Global Hepatitis Report by the WHO in 2017, the prevalence of chronic HCV infection (viremic infection) in 2015 was estimated to be 1.0%. This prevalence was 0.7%, 0.5%, and 2.3% in the Western Pacific, South Eastern Asian, and Eastern Mediterranean regions respectively. The incidence rate of HCV infection in 2015 was estimated to be 23.7 per 100,000. This rate was 6.0, 14.8, and 62.5 in the Western Pacific, South Eastern Asian, and Eastern Mediterranean regions respectively.[1]

In many countries, the incidence of HCV infection increased between the 1960s and 1970s, and then decreased in the 1990s with the introduction of HCV screening tests in blood transfusion institutions. In 2016, the World Health Assembly proposed the elimination of viral hepatitis as a public health threat by 2030 and called for action plans in each country. However, the trend in the incidence rate of HCV infection varies among nations. The age-standardized rate decreased from 87.9 in 1990 to 55.0 in 2019 in China and from 56.[2] in 1990 to 50.7 in 2019 in India. In contrast, the rate increased from 56.2 in 1990 to 66.5 in 2019 in the USA. Improvements in medical conditions and blood screening have influenced the reduction of HCV infection in developing countries. On the other hand, the increase in intravenous drug use has led to an increase in HCV infection in developed countries like the USA.2 Not only in Western countries but also in Asian-Pacific countries, the prevalence of HCV infection among intravenous drug users has been reported as high as 24% to 51%.[3] Therefore, it is important to control HCV infections among intravenous drug users in order to achieve the WHO's 2030 goals in the Asian-Pacific region.

The Polaris Observatory HCV collaborators reported a global change in HCV prevalence between 2015 and 2020. They estimated a global prevalence of viremic HCV infection of 0.7%, corresponding to 56.8 million infections as of the beginning of 2020. This represents a reduction of 6.8 million viremic infections from a revised 2015 estimate of 63.6 million viremic infections. The change in viremic infections resulted from the addition of 7.5 million new chronic infections, the subtraction of 8.7 million cured infections, and the subtraction of 5.5 million deaths. The prevalence was 0.6%, 0.5%, and 1.4% in the Western Pacific, South Eastern Asian, and Eastern Mediterranean regions respectively.[4]

Notably, when the cascade of care was estimated for 2015-2019 and 2020, the proportion of individuals ever diagnosed among those infected was 33% and 23% respectively, and the proportion of those diagnosed who received treatment was 45% and 5% respectively. This decrease in the proportion of diagnosis and treatment might be attributed to the completion of large-scale national HCV elimination

programs, such as in Egypt, the cessation of patient screening after treating those already diagnosed, and the negative impact of the COVID-19 pandemic. Without an accelerated effort to eliminate HCV infections, the global annual number of new chronic infections was expected to remain constant, and end-stage outcomes were expected to increase by 14-17% relative to 2020 by 2030. The estimated proportion of the cascade of care for HCV infection varied among nations in the Asian-Pacific region. The proportion of diagnosis among HCV infections was 76.3% in the high-income Asia Pacific area (Japan, Korea), and 87.0% in Australia, while it was only 13.9% in southeast Asia and 16.5% in south Asia. The annual proportion of treated viremic patients in 2020 was 6.1% in the high-income Asia Pacific area, 5.6% in Australia, but only 0.7% in southeast Asia and 0.6% in south Asia.[4]

Among patients with acute hepatitis C, 15-45% experience spontaneous virologic clearance, while the remainder progress to chronic infection. The high rate of spontaneous HCV clearance in the Asia-Pacific region may be due to the high prevalence of the favorable IL28 genotype. Generally, 20-30% of patients with chronic infection are known to develop cirrhosis within 25-30 years. Once cirrhosis is established, the annual incidence of HCC is known to be 1-4%.[5] While factors like age at infection, duration of infection, alcohol consumption, HIV co-infection, male gender, and obesity are associated with fibrosis progression, most HCV patients, if left untreated, are expected to develop cirrhosis around the age of 65, regardless of their age at infection.[6] Additionally, HCC often develops in individuals over the age of 60 with HCV infection, regardless of their exposure to the virus.[7] This suggests the possibility of a critical age point beyond which chronic HCV infection progresses.

In summary, the global prevalence of HCV has decreased from 2015 to 2020 due to extensive screening and the introduction of effective treatments. However, this trend has stagnated due to challenges in linking diagnosis, treatment, and follow-up in 2020. Considering the expected increase in advanced outcomes of chronic infection in the older population, there is an urgent need for accelerated efforts in national-level decision-making to eliminate HCV infections.

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Clinical Impacts of Epidemiological Growth of NAFLD in Asian-Pacific Region

Young Youn Cho

Chung-Ang Univ., Korea

Introduction

There was an epidemiological growth of non-alcoholic fatty liver disease (NAFLD) in the Asian Pacific region. This review outlines the prevalence and clinical impacts of NAFLD in the Asian Pacific region.

Increase of NAFLD in Asian Pacific region

The estimated prevalence of NAFLD is approximately 30% worldwide, and this prevalence is increasing globally. A recent study indicated that the worldwide prevalence of NAFLD has risen from 26% to 38% over a 10-year period. The prevalence of NAFLD in the Asian Pacific region is reflecting a similar upward trend. However, the studies conducted were heterogeneous, with limited population-based studies included in the analysis. Non-alcoholic steatohepatitis (NASH) represents a progressive form of non-alcoholic fatty liver disease (NAFLD), characterized by inflammation and damage to liver cells. The prevalence of NASH exhibits similarities across Asian Pacific countries, with rates such as 5.4% in South Asia, 5.3% in Southeast Asia, 4.8% in East Asia, and 4.5% in Oceania.

Cause of epidemiologic change

Rapid urbanization and the adoption of Western dietary patterns are believed to be contributing factors to the increasing prevalence of NAFLD in the Asian Pacific region. These shifts have resulted in a rise in obesity rates, a key risk factor for NAFLD. Genetic background can also contribute to NAFLD development. For instance, the PNPLA3 GG gene variant is more prevalent among East Asians, who generally exhibit healthier metabolic profiles. This genetic factor could potentially account for the comparable NAFLD prevalence across countries and the prevalence of lean NAFLD being higher in the Asian Pacific area.

Clinical impact

The incidence of liver-related complications, including cirrhosis and hepatocellular carcinoma (HCC) stemming from NAFLD, has been on the rise globally. Data extracted from the Global Burden of Disease 2009-2019 study unveiled an escalation in global liver complications linked to NAFLD. Notably, the Asia Pacific regions contribute to nearly half of this global burden. Several studies suggest that cases of liver cirrhosis associated with NAFLD are projected to double in many countries from 2016 to 2030. Furthermore, a comprehensive global analysis has indicated an increasing occurrence of primary liver cancer attributed to non-alcoholic steatohepatitis (NASH), particularly among older age groups.

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Cure of Viral Hepatitis: Definition and Sub-Classification

Hyun Young Woo

Pusan National Univ., Korea

There are five main strains of the hepatitis virus, referred to as types A, B, C, D and E. In particular, types B and C lead to chronic disease in hundreds of millions of people and together are the most common cause of liver cirrhosis, liver cancer and viral hepatitis-related deaths. The goal of treatment for hepatitis C is to cure the disease and prevent long-term liver damage. There is currently no effective vaccine against hepatitis C. However, there are effective treatments for hepatitis C. Direct-acting antiviral medicines (DAAs) can cure more than 95% of persons with hepatitis C infection. Generally, undetectable HCV RNA 12 or more week after completing treatment represents sustained virologic response and virologic cure. The primary goal of therapy for CHB is to improve survival by preventing cirrhosis, hepatic failure, hepatocellular carcinoma (HCC) and liver-related death. However, these are too long-term outcome that cannot be known in a short period of time. Therefore, there need shorter term or intermediate endpoint to substitute these long-term outcomes. Of all surrogate endpoints, HBsAg loss is considered to be the most relevant because HBsAg seroclearance is associated with sustained off-treatment improvement in clinical outcomes. Additionally, HBsAg loss has been shown to have lower rate of disease reactivation, and once achieved, there is no further requirement for other therapy. And it is easy to measure with standardized and wild available assay. However, covalently closed circular DNA (cccDNA) and integrated HBV DNA is still in the nucleus of hepatocytes even after loss of HBsAg. The presence of HBV cccDNA and integrated HBV DNA confers the risk of viral reactivation and hepatocellular carcinoma. A sterilizing cure may be a more perfect concept. Here, all traces of HBV infection would be eliminated, including cccDNA and integrated HBV DNA. This endpoint is ideal but currently impossible to achieve, as we currently lack therapies that can eliminate both cccDNA and integrated HBV DNA and lack commercial and standardized assays for quantifying cccDNA and integrated HBV DNA. An alternative and less desirable goal is a partial cure, defined as HBsAg positive, HBeAg negative with HBV DNA persistently <LLOD, 24 weeks off-treatment. Although long-term sustained off-treatment HBV DNA suppression is also associated with improved clinical outcomes similar as HBsAg loss, in patients with cirrhosis, it is not reliably sustainable, and there is a 15 to 40 percent chance of the disease being reactivated over a lifetime. Therefore, in present. functional cure, defined as HBsAg loss with or without development of anti-HBs and HBV DNA less than the Lower Limit of Detection (<LLOD) 24 weeks off-treatment is proposed as most preferred realistic goal.

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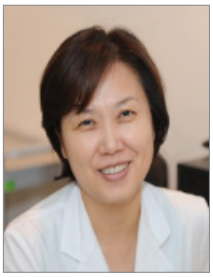

Overview of Barriers to HBV Cure

Eun Young Cho

Wonkwang Univ., Korea

The Hepatitis B virus (HBV) is the major cause of both acute and chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Although an effective vaccine has been available for approximately 40 years, HBV continues to be a significant global health concern. It is estimated that 3.5% of the global population, equating to 2.57 million individuals, suffers from chronic HBV infection.[1] Administering the appropriate antiviral therapy for chronic HBV is crucial. By inhibiting HBV replication, antiviral therapy can alleviate hepatic inflammation, normalize serum ALT levels, enhance liver fibrosis recovery, reduce the incidence of HCC, and decrease liver-related mortality.[2] Nonetheless, the antiviral treatments available at present cannot fully eradicate the virus.

The principal obstacle to curing HBV is the presence of covalently closed circular DNA (cccDNA). While the commonly used nucleos(t)ide analogue (NA) can impede the RNA transcription process emanating from cccDNA, it cannot eliminate cccDNA itself. Consequently, cccDNA remains a significant factor behind HBV reactivation post-NA cessation. Given that cccDNA plays a pivotal role in viral persistence, identifying all host factors that influence cccDNA formation and comprehending the rcDNA-to-cccDNA conversion process are vital to eliminating HBV. Also, the invention of drugs targeting cccDNA directly is essential to curing hepatitis B.[3]

Another significant challenge in curing HBV is the presence of integrated HBV DNA, which acts as a reservoir for HBV antigen production. The integration of HBV occurs early during the chronic phase of the HBV infection and intensifies with the infection's duration. Recent studies suggest that extended viral suppression might counteract this trend to some extent.[4] Integrated HBV DNA can instigate hepatocarcinogenesis through mechanisms such as insertional mutagenesis, heightened genomic instability, or the expression of viral oncogenes, including the HBx protein. It may also be a causative agent for HCC, even following HBsAg loss.[5] In the late phase of HBV infection (HBeAg -), over 50% of HBsAg originates from integrated HBV DNA. Hence, integrated HBVDNA should also be a treatment target for HBV cure.[6]

Furthermore, a compromised innate and adaptive immune response to the HBV virus presents a major barrier to its cure. The elevated presence of circulating HBsAg leads to the downregulation of HBsAg- and HBeAg-specific T-cell immunity[7] and suppression of innate immunity, primarily through the dysfunction of dendritic cells and natural killer cells, resulting in chronic infection.[8,9] Therefore, implementing immunomodulatory therapies to rejuvenate the immune response to HBV is under exploration. Such therapies are vital to achieve a functional cure by eliminating infected hepatocytes and/or preventing the infection of new ones.[10]

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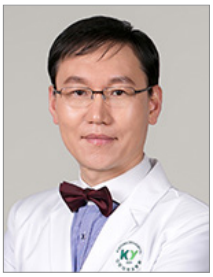

Overview of Barriers to Hepatitis C Cure

Tae-Hee Lee

Konyang Univ., Korea

Viral hepatitis B and C affects 325 millions of people globally. The number of the patient with viral hepatitis C is about 71 million in the world, posing global health burden.[1] The World Health Organization (WHO) have the goal for the elimination of viral hepatitis B and C by 2030, which contains a reduction of new infection by 90%, death by 65%, increase of diagnosis to 90% and treatment to 80% of eligible patients (Global health sector strategies 2022-2030).[2] Although the direct acting antivirals (DAAs) are potent to hepatitis C virus infection, (even, pan-genotypic DAAs have about 95% SVR rate), interferon-free DAAs treatment rate remains suboptimal (52.3% overall, 32.3% in HCC patients).[3]

There are many barriers to hepatitis C treatment, including patient factors, provider factors and systemic factors.[4] Patient Factors are knowledge and awareness, non-adherence, economic and social pressure, fears of treatment, psychiatric diseases, injection drug use, medical comorbidities, stigma and discrimination, lack of health insurance. Provider Factors are composed of knowledge and awareness, specialist referral and availability, communication issue. Systemic Factors contain government policy, payer's restriction, high cost of treatment, diagnosis of hepatitis C. To overcome the barriers, many solutions are proposed and carried out (Table 1).[5]

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Table 1. Barriers and proposed solutions to increase HCV treatment

Layer	Barriers	Proposed solution
Patient	• Access to healthcare professionals • Competing health priorities/ Comorbidities • Poor HCV knowledge • Asymptomatic infection • Fears about treatment • HCV stigma/ Discriminations	• Community education • Engage communities to promote testing • Create treatment literacy materials
Providers	• Limited knowledge/ Treatment not addressed • Treatment misconceptions	• Training programs • Simplify model of care • Decentralise HCV care to primary care
Systemic	• Insufficient providers who can treat HCV • National treatment guidelines • Unaffordable diagnostic tests • HCV medication high price • Lack of national/regional HCV strategies	• Strong political commitment • Funding to start HCV programs • Decrease cost of care • Estimate disease burden • Identify high risk groups

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APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

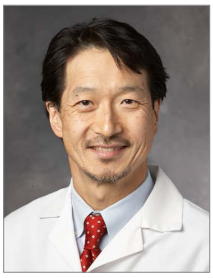
"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 1 | Thursday, Sept. 21, 2023

President's Choice Lecture

Chair:
Si Hyun Bae (The Catholic Univ. of Korea, Korea)



A Bold Plan to Eliminate Liver Disease

W. Ray Kim

Stanford Univ., USA

Liver disease is an important cause of morbidity and mortality globally. In the adjacent table, the number of deaths from cirrhosis worldwide was estimated to be approximately 1.5 million, men outnumbering women by 2:1.

Progresses have been made in the patient care for chronic liver disease in the past three decades ranging from antiviral therapeutics to endoscopic management of portal hypertension to liver transplantation. As ground-breaking as these advances have been, their impact has been limited to patients with well-established diagnosis of chronic liver disease, often advanced liver disease and cirrhosis. In order for the large impact of chronic liver disease to be mitigated, systematic efforts are needed to diagnose and treat liver disease early in the course and prevent patients from developing advanced fibrosis and complications of liver cirrhosis.

In public health, these efforts represent secondary prevention, namely screening to identify diseases in the earliest stages before signs and symptoms of disease develops. For us as hepatologists, we do not have access to these individuals and it is essential for us to engage primary care providers to take on these roles. In this context, the role of hepatologists needs to expand to include peer (and patient) education and developing partnerships as well as research in healthcare delivery and implementation.

Number of deaths from chronic liver disease and cirrhosis from the Global Burden of Disease 2019 data (numbers in thousands)

Deaths	Total	Female	Male
HCV	395	127	268
HBV	331	94	237
Alcohol	372	97	275
NAFLD	134	62	72
Other	240	123	117
Total	1472	503	969

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Symposium 1-1. Hepatitis Elimination by 2030: Where Are We Now?

Chairs:

Diana A. Payawal (Fatima Medical Univ. Philippines)
Dong Jin Suh (Daehang Hospital, Korea)

HBV 2023: New Therapeutic Strategies against an Old Foe

Sang Hoon Ahn

Yonsei Univ., Korea

Hepatitis B virus (HBV) infection remains a significant public health concern, leading to noteworthy levels of illness and death globally, and affecting approximately 292 million individuals worldwide. With advancements in antiviral therapy, the current treatment approach to chronic hepatitis B (CHB) involves employing nucleos(t)ide analogs (NAs) to inhibit the replication of HBV DNA. This results in a decreased risk of developing cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths, all while upholding a favorable safety profile. However, a majority of patients require prolonged and continuous treatment to achieve sustained suppression of HBV DNA, as NAs are incapable of effecting a functional cure for HBV infection. Moreover, taking into consideration both the risks stemming from the untreated patients in the "grey-zone" beyond the scope of current international treatment guidelines in the past decade, and the hazards posed by the remaining viral factors, such as HBV DNA integration into the host cell, concerns persist concerning the potential long-term development of HCC. However, efforts are being made to overcome these limitations.

The evolving therapeutic strategies entail the expansion and simplification of the guideline to encompass patients in the "grey-zone" for the treatment criteria. East Asia expert opinion on simplifying treatment criteria recommends antiviral therapy for patients with (a) HBV DNA ≥ 2000 IU/mL and ALT ≥ 1× ULN; (b) HBV DNA ≥ 2000 IU/mL, ALT <1× ULN and ≥ F2 fibrosis and/or ≥ A2 necroinflammation occurs; (c) cirrhosis and detectable HBV DNA; or (d) HBV DNA ≥ 2000 IU/mL, ALT <1× ULN and a family history of cirrhosis or HCC, extrahepatic manifestations or age >40 years, regardless of HBeAg status.[1] Retrospective studies have unveiled that the non-negligible proportion of patients who did not meet treatment criteria had a significant disease, such as significant fibrosis with elevated HBV DNA despite being within the upper limit of normal range (ULN) of alanine aminotransferase (ALT).[2,3] Significantly, a considerable proportion (33.5 - 64.0%) of patients developing HCC did not conform to current international treatment criteria and the markedly elevated cumulative incidence of untreated patients in an indeterminate phase (vs. those in an inactive phase) have emphasized the need for expansion of treatment criteria.[4-7] Moreover, the result from a recent randomized controlled study with paired liver biopsy, that the 3-year intervention with NAs for patients in the "grey-zone" achieved a significantly greater reduction in distinct viral-host DNA integration, suggests that the expansion of treatment criteria can reduce HCC development not only attenuating fibrosis progression but also suppressing the direct viral-host interaction.[8] Future prospective studies merit investigation employing these simplified criteria.

Simultaneously, strategies employing newly developed drugs are fostering optimism for attaining a functional cure for hepatitis B virus infection. These approaches can be categorized into three groups:

replication inhibitors (including viral entry inhibitors, HBV polymerases, and capsid assembly inhibitors), agents inducing antigen burden reduction (such as antisense oligonucleotides and siRNAs), and immune modulators.[9] Studies have proposed a dual combination of the newly developed drugs with existing NAs to diminish HBsAg quantitation.[9,10] Furthermore, ongoing clinical trials exploring triple combinations involving the three therapeutic categories—viral replication suppression, viral antigen burden reduction, and immune enhancement—offer initial data on efficacy and insights into their feasibility and potential for reducing HBsAg quantitation.[9,10] Various therapeutic strategies and agents have yielded functional cure outcomes, though largely in a limited subset of patients. While multiple pathways exist towards achieving this goal, identifying the most effective strategy remains elusive thus far.[9-11]

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HCV 2023: The Road to Elimination of HCV

Yasuhito Tanaka

Kumamoto Univ., Japan

Viral hepatitis is a major contributor to the global disease burden and shows that this disease requires a stronger national and international response. However, huge number of undiagnosed carriers of hepatitis C virus (HCV) still remains worldwide. Biomedical advances have led to efficacious treatments for HCV that could be delivered at scale, but it is necessary to scaling up of screening test and treatment to reduce mortality.

In Japan, there are many chances to have infection screening tests. These tests are carried out prior to operation or blood transfusion in routine. The main purpose of these routine preoperative infection screening tests is to prevent and control healthcare-associated infection. Furthermore, many of these tests are performed in non-specialized hospitals for liver disease. In consequence, hepatitis virus carriers who are detected by screening tests, have not been given adequate information.

To develop an effective regional network for hepatitis treatment, we attempt to organize the referral system which is composed of the core center (Kumamoto University Hospital), its affiliated hospitals and community hospitals or clinics. Target community hospitals or clinics are non-specialized for liver disease, in which preoperative infection screening test are performed in routine. We design the primary endpoint of this study, to increase follow-up rate and treatment rate of HCV-positive patients who are proved by screening test. Secondary endpoint of this study is to organize a specialized hospitals-nonspecialized hospitals/clinics referral system as multi-center system. Kumamoto University hospital is the core center of the regional network for hepatitis treatment in Kumamoto prefecture. We also have affiliated hospitals as specialized institutions for liver disease in second medical care zones. We aim to formalize this system not only in Kumamoto city, but also in whole Kumamoto prefecture. In consequence, our proposed system would be a useful system for patients with HCV-related liver disease to be free from their anxiety and improve long-term care.

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Optimizing Hepatitis B and C Treatment in Resource-Limited Settings

Diana A. Payawal

Fatima Medical Univ., Philippines

Global Care Cascade for Chronic Hepatitis B and C Virus Infection

Ming-Lung Yu

National Sun Yat-sen Univ., Taiwan

In 2016, the World Health Assembly adopted the Global Health Sector Strategy (GHSS) on viral hepatitis. The World Health Organization (WHO) set ambitious targets for the elimination of viral hepatitis as a public health threat by 2030, including hepatitis B (HBV) and hepatitis C (HCV). They are defined as a 95% reduction in incidence and 65% reduction in mortality for HBV and a 90% reduction in incidence and 65% reduction in mortality for HCV by 2030, compared with the 2015 baseline. In line with the GHSS, WHO has developed this interim guidance and framework for countries and other stakeholders seeking validation of elimination of viral hepatitis as a public health problem. Overall, the guidance suggests the use of absolute impact targets to validate elimination at the national level (instead of, although equivalent to, the relative reduction targets originally defined in the 2016 GHSS) in combination with a set of programmatic targets.

The main impact indicators and targets for measuring HBV elimination are defined as 1) ≤0.1% HBsAg prevalence in those aged 5 years or less 2) an HBV-related annual mortality rate of ≤4 per 100,000 persons. To achieve the targets, ≥90% of HBV patients should be diagnosed, ≥ 80% of patients diagnosed and eligible for treatment should be treated, and ≥90% of newborns should be covered with hepatitis B vaccine (3-dose and timely birth-dose). The main impact indicators and targets for measuring HCV elimination are defined as 1) ≤5/100,000 annual incidence (general population) and ≤2/100 annual incidence (PWID) 2) an HBV-related annual mortality rate of ≤2 per 100,000 persons. To achieve the targets, ≥ 90% of HCV patients should be diagnosed, ≥ 80% of patients diagnosed and eligible for treatment should be treated.

Progress was being made through increased vaccination coverage, especially in regions with high prevalence, and the availability of antiviral treatments to manage chronic HBV infection. However, challenges included gaps in vaccination coverage, especially among adults and high-risk groups, and limited access to diagnostics and treatment in some regions. In 2019, only 10.3% HBV people living with HBV were aware of their infection status and 22.7% of those diagnosed HBV received treatment. For HCV, progress was being made with the development of highly effective direct-acting antiviral (DAA) therapies, which offered cure rates exceeding 95%. Many countries were implementing programs to increase HCV testing, diagnosis, and treatment. However, challenges included identifying undiagnosed cases, ensuring access to testing and treatment, and addressing stigmatization and discrimination. The diagnosis coverage was only 21% and the overall treatment coverage was only 13% globally. Overall, an estimated 89% of HBV infections and 78% of HCV infections remain undiagnosed.

The global efforts toward the elimination of HBV and HCV were progressing, but challenges remained. A new global strategy for 2022-30 should be implemented urgently to scale up the screening, diagnosis, prevention and treatment of viral hepatitis.

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State-of-the-Art Lecture 1

Chair:
Masao Omata (The Univ. of Tokyo, Japan)

A 30-Year Journey of HCV Research: From Discovery to a Cure

Raymond T. Chung

Harvard Univ., USA

The origin of non-A, non-B hepatitis. Although the first successful human blood transfusion occurred over two centuries ago, the procedure did not gain widespread acceptance until World War II. Shortly thereafter cases of post-transfusion hepatitis began to be reported in the medical literature.[2] Following the discoveries of HBV in 1965 and HAV in 1973 and the switch from paid blood donors to an all-volunteer blood donor system, cases of post-transfusion hepatitis declined dramatically from 33% to 6%. However, cases continued to persist that were not due to HAV or HBV, so-called non-A, non-B hepatitis.[3] It was during this period that Dr. Alter became involved and conducted seminal natural history studies of post-transfusion hepatitis. Key to later success was the decision to define cases based on elevated serum alanine aminotransferase levels, recognizing that not all cases of post-transfusion hepatitis presented with jaundice. This fortuitous decision together with the meticulous collection of samples from both blood donors and recipients, allowed Dr. Alter to establish a carefully pedigreed series of post-transfusion non-A, non-B cases that would later prove invaluable in confirming that the HCV was the causative agent of non-A, non-B hepatitis. Dr. Alter along with his collaborators used these samples to conduct pioneering chimpanzee inoculation studies to demonstrate that the likely etiological agent was a bloodborne transmissible agent.[4] Of importance, natural history studies conducted by Dr. Alter and others demonstrated that most cases of non-A, non-B hepatitis became chronic and a proportion developed cirrhosis.[5]

Discovery of HCV. Dr. Michael Houghton joined the search for the etiological agent of non-A, non-B hepatitis in 1982 after he was recruited to Chiron. He employed multiple molecular approaches to identify the etiological agent including a shotgun cloning strategy that involved creation of a bacterial 'cDNA library' derived from infected human and chimpanzee liver and plasma (on the assumption that some clones were likely to contain nucleic acid of viral origin).[6] The library was screened by demonstration of specific hybridization of a radioactive probe that was complementary in sequence and derived from infected but not uninfected source material and cDNA probes from known viruses that might share sequence similarity with the non-A, non-B agent. Despite screening millions of clones, these approaches proved unsuccessful. More conventional approaches to propagate the non-A, non-B agent in culture systems and to visualize the virus by electron microscopy or to separate nucleic acid on electrophoretic gels loaded with chimpanzee or human liver or blood with the aim of identifying high molecular weight RNA and DNA viral genomes were also unsuccessful. Instead of trying to identify the nucleic acid with a complementary nucleic acid probe, a blind cDNA immunoscreening approach was next used in which the protein product of the cloned nucleic acid was identified using an antibody. Using a high titer chimpanzee plasma pool and serum from a patient with active hepati-

tis (the assumption being that more active disease would be associated with higher antibody levels) led to the identification of a single, small clone of ~150 base pairs which was shown to be derived from the genome of the hepatitis C virus.[7] This clone was used to identify the remainder of the viral genome and to develop an antibody test for the virus. This antibody was also used to correctly identify Dr. Alter's coded samples and a majority of samples from patients with non-A, non-B hepatitis procured from different geographical regions.[8] The etiological agent of non-A, non-B hepatitis had been found and was christened HCV.

Characterizing HCV. Following the identification of HCV, initial efforts to establish an in vitro culture model system using clinical HCV isolates to infect various cultured hepatocytes were unsuccessful. Dr. Rice demonstrated this was due to the absence of 3' sequence of the initial cloned viral genome. However, a corrected viral isolate was also unable to replicate efficiently in cell culture. Dr. Rice then developed a subgenomic replicon consisting of the HCV non-structural proteins and an internal ribosome entry site (IRES) sequence that was able to replicate in culture albeit at low level.[9] Replication was further enhanced through the introduction of a series of cell culture adaptive mutations and identification of a human hepatoma cell line (Huh-7.5) that was highly permissive for replication of subgenomic and full-length HCV RNAs.[10] Later a viral isolate from a Japanese patient with fulminant hepatitis yielded high level of viral replication without the need for adaptive mutations and more importantly infectious virions in the culture media.[11] This now permitted studies on the entire viral replication cycle and screening of therapeutic compounds to be conducted.

In tandem with this ground-breaking virological work, efforts were ongoing to develop effective treatments for chronic HCV infection. Initially, interferon alfa was tried but with limited success. Advancements in therapy were initially achieved by the addition of ribavirin to standard interferon alfa and then later the development of a long-acting pegylated form of interferon alfa.[12] Deciphering the crystal structure of the non-structural proteins together with the availability of the replicon system allowed the screening a large variety of inhibitor compounds. This ultimately led to the development of safe and effective all oral therapy. Virological cure of all HCV strains could be achieved in over 95% of patients with 8 to 12 weeks of treatment.[13]

From the first description of non-A, non-B hepatitis to the identification of HCV and the development of curative therapy has spanned a short period of three decades. In a few short years, we have already seen significant improvements in liver related and all-cause mortality in the aftermath of DAA implementation. The availability of DAAs has also enabled the productive use of HCV infected donor organs in both infected and uninfected recipients. This achievement represents a remarkable triumph of biomedical science and fittingly resulted in the awarding of the Nobel Prize to Drs. Alter, Houghton, and Rice.

However, the work is not yet finished. Unfortunately, only a fraction of the estimated 70 million persons with chronic HCV infection have been diagnosed and received curative therapy. The goal is now to identify and treat the remaining cases. To this end the World Health Organization has challenged the stewards of the world's health systems to eliminate chronic HCV infection by 2030. This will require creative models of health care in different geographical regions to enhance case identification, including point of care testing, prevention of transmission, and universal access to curative therapy. It will also likely require the development of a broadly protective HCV vaccine, as curative therapy alone will likely be insufficient to truly eradicate HCV. For those with chronic HCV and advanced fibrosis, cure of HCV will not suffice to eliminate the risk for hepatocellular carcinoma (HCC). Additional avoidance of cofactors such as fatty liver, alcohol, iron overload and chronic HBV will be essential.

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APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 1 | Thursday, Sept. 21, 2023

Keynote Lecture 1. Viral Hepatitis Elimination: Where Do We Stand? It Has Already Reached Halfway by 2030

Chairs:

Chun-Jen Liu (National Taiwan Univ., Taiwan)
Kwang Cheol Koh (Sungkyunkwan Univ., Korea)

Notable Milestones Achieved towards Viral Hepatitis Elimination to Date

Jose D. Sollano

The Univ. of Santo Tomas, Philippines

Major progress in eliminating hepatitis C virus (HCV) infection has been facilitated by the introduction of direct acting antivirals (DAAs) in 2013. The WHO and many countries have already implemented, albeit unevenly, successful strategies to mitigate HCV transmission, e.g., safe transfusion practices of blood and blood products, raising awareness on the dangers of IV drug use and needle stick injury, needle replacement programs, safe sex, reimbursed treatments, etc. The current strategy of HCV elimination in many locales starts with case finding and efficient treatment of the at-risk population so that a successful microelimination of HCV infection in these selected cohort may later lead to an HCV macroelimination outcome.

An effective recombinant vaccine is available against the hepatitis B virus (HBV) since 1986. Countries which have implemented a successful vaccination program, e.g., UK, Taiwan, have already reported elimination of mother-to-child transmission of HBV infection. The WHO has set an ambitious goal of reducing the HBsAg seropositivity in newborns to 1% by 2030. Many countries are on target with such lofty goals but many more countries need to step up their vaccination campaigns. In addition, treating HBV-infected pregnant mothers with nucleotide analogues have contributed to these efforts. A combined program of HCV, as well as, HBV case finding and reimbursed treatments for/of infected individuals are huge steps in controlling successfully these viral infections.

Only HBV-infected individuals may acquire hepatitis delta virus (HDV) infection. Efficient control of HBV infection augurs well for the control of HDV spread.

The COVID pandemic, however, has impacted negatively on the initial successes we have achieved thus far. A study in 2021 estimated that until 2030 there may be 900,000 missed new diagnoses of HCV infection and a reduction of about 750,000 possible treatments delivered largely due to the global pandemic -resulting in approximately 448,00 excess HCC cases and 72,300 excess liver-related deaths during the decade of 2020-2030.

The frequent route of infection of the hepatitis A virus (HAV) and hepatitis E virus (HEV) is the fecal-oral route, although HEV genotypes 3 & 4 are transmitted by zoonosis. Improvements of sanitary practices therefore are key steps in preventing infection. An effective vaccine is available against HAV and is highly recommended in patients with concomitant chronic HCV and/or HBV infection and in non-immune people traveling to areas of high endemicity. A vaccine against HEV is also available in China since 2011 with reported very good efficacy in preventing symptomatic acute hepatitis E. The overall duration of protection offered by the vaccine and its safety in patients with other liver conditions, as well as, in pregnant women need further elucidation.

Efforts and Strategy to Accelerate Progress towards Viral Hepatitis Elimination by 2030

Jinlin Hou

Southern Medical Univ., China

It Is Time for a Simplified Approach to Hepatitis B Elimination

Young-Suk Lim

Univ. of Ulsan, Korea

A prospective cohort (REVEAL) study[1] showed that the risk of hepatocellular carcinoma (HCC) increase with increasing levels of baseline serum hepatitis B virus (HBV) DNA up to 10^6 copies/mL (about 5 $\log_{10}$ IU/mL), irrespective of serum alanine aminotransferase (ALT) levels and HBeAg status, in chronic hepatitis B (CHB) patients. Nonetheless, the association between very high HBV DNA levels (especially >6 $\log_{10}$ IU/mL) and HCC risk remains unclear, especially in middle-aged and old HBeAg-positive patients with normal ALT levels. Accordingly, antiviral treatment of the patients with high HBV DNA and normal ALT levels is controversial.

Recently we have analyzed the association between a broad range of serum HBV DNA levels and long-term HCC risk in a total of 6949 HBeAg-positive and HBeAg-negative, non-cirrhotic, treatment-naïve CHB patients who are not generally indicated for antiviral therapy by current practice guidelines because of no significant ALT level elevation.[2] We found that the association between HBV DNA levels and HCC risk is not linear but parabolic in these patients. The HCC risk was highest at moderate HBV DNA levels 6.3 $\log_{10}$ IU/mL, with decreasing HCC risk at higher and lower HBV DNA levels. Very high HBV DNA levels (>8 $\log_{10}$ IU/mL) showed the lowest HCC risk which was not significantly different from that of very low HBV DNA levels (≤4 $\log_{10}$ IU/mL). The similar findings were consistently observed in all age subgroups.

Our another study have demonstrated that untreated non-cirrhotic HBeAg-positive CHB patients with persistently normal ALT levels were associated with significantly higher risks of HCC than the immune-active phase patients treated with nucleos(t)ide analogs for elevated ALT levels.[3] Further, untreated non-cirrhotic HBeAg-negative CHB patients with high viral load and no significant ALT elevation had higher risks of clinical events than treated HBeAg-negative active hepatitis phase patients with elevated ALT.[4]

Based on our recent findings, we suggest to use the terms "high replication phase," "moderate replication phase," and "low replication phase", which may help to distinctively indicate the HCC risk and the necessity of treatment in CHB patients. Since the highest HCC risk is at moderate viral load, CHB patients who persistently have moderate levels of HBV DNA (4-8 $\log_{10}$ IU/mL) may be indicative of antiviral treatment regardless of HBeAg and ALT elevation to reduce the risk of HCC. However, most patients with HBV DNA >8 $\log_{10}$ IU/mL may eventually have progressive decline in the HBV DNA levels and subsequently increasing risk of HCC. Therefore, to prevent the risk of HCC to the greatest possible degree, our data suggest that antiviral treatment may also have to be initiated with HBV DNA levels >8 $\log_{10}$ IU/mL, regardless of ALT levels, especially in patients with CHB older than 30 years.

It has been unclear whether the level of serum HBV DNA at baseline impacts the on-treatment risk of HCC in HBeAg positive, non-cirrhotic patients with CHB. We found that on-treatment HCC risk increased in-

crementally with decreasing baseline HBV DNA levels in the range of ≥5.00 $\log_{10}$ IU/mL in those patients.[5] Therefore, early initiation of antiviral treatment with a high viral load (≥8.00 $\log_{10}$ IU/mL) may maintain the lowest risk of HCC in those patients.

We also found that starting antiviral therapy in immune-tolerant phase is cost-effective compared with delaying the treatment until the active hepatitis phase in CHB patients, especially with increasing HCC risk, decreasing drug costs and consideration of productivity loss.[6] Simplifying and expanding treatment eligibility for CHB would save many lives and be highly cost-effective when combined with high diagnostic rates.[7]

Collectively, a simplified treatment algorithm may have to be recommended to initiate treatment in all CHB patients older than 30 years with serum HBV DNA levels >2,000 IU/mL, regardless of HBeAg status and ALT levels. Accumulating data on the long-term efficacy and safety of anti-HBV drugs with high potency, high genetic barrier to resistance, and decreasing cost may facilitate earlier treatment initiation.

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PG Course 1. On the Way to HBV Elimination, What Is a Recent Issue?

Chairs:

Marc G. Ghany (NIH, USA)
George Lau (Humanity and Health Medical Group, Hong Kong)
Kwang-Hyub Han (CHA Univ., Korea)

When to Stop Nucleos(t)ide Analogues: Risks and Benefits

Jordan Feld

Univ. of Toronto, Canada

With the recognition that discontinuation of nucleos(t)ide analogues (NA) can lead to hepatitis B surface antigen (HBsAg) clearance in some individuals, there has been increasing interest in exploring NA withdrawal as a therapeutic approach. Although NA withdrawal may be beneficial, it can also lead to rapid relapse of active hepatitis, that at least on occasion, can lead to fulminant liver failure. The challenge for clinicians is determining whether a given patient is likely to benefit or be harmed by NA withdrawal.

The early studies of NA withdrawal documented that virological relapse is almost universal after stopping treatment and typically occurs 4-8 weeks after NA cessation. However, what happens after the initial rise in HBV DNA is very variable. In some patients, HBV DNA levels decline to low or undetectable levels and patients remain with inactive disease that may progress to HBsAg loss or functional cure over time. However, in other patients the rise in HBV DNA is followed by a flare of ALT that can lead to active hepatitis and rarely go on to precipitate liver failure. The rates of these different outcomes vary widely across studies, raising significant challenges for clinical management.

Early small, controlled trials reported rates of HBsAg loss as high as 20% after NA withdrawal whereas other similar sized trials found very low rates of HBsAg loss. As data accumulated, it became clear that host and viral characteristics clearly influence the outcome after NA withdrawal and likely explained the differences reported in the first trials. To further understand the predictors of outcome, the RETRACT-B cohort was developed that brings data from sites around the world after NA withdrawal to identify predictors of HBsAg loss and negative outcomes. With a large population (>1500), this study was able to tease apart important predictors of outcome after NA withdrawal. On the host side, the most important predictor of clearance is race/ethnicity, with Caucasians having a higher chance of clearance than Asians (HR 6.8). Less important factors associated with HBsAg loss were older age and tenofovir rather than entecavir therapy. On the viral side, quantitative HBsAg loss at the time of withdrawal is critical. Not surprisingly, those with low qHBsAg levels are more likely to clear. Using the data from the RETRACT-B study, there was a clear interaction between qHBsAg level and race/ethnicity. In Caucasian patients with HBsAg levels below 1000 IU/mL, the cumulative incidence of clearance by 4 years was 41% compared to just 4% in those with HBsAg levels above this threshold. In contrast, for Asian patients, if qHBsAg levels were above 100 IU/mL only 2% of patients cleared HBsAg during follow-up whereas 33% of patients lost HBsAg if they had a qHBsAg<100 IU/mL at NA withdrawal. From these data, the authors proposed a strategy of considering NA withdrawal in Caucasian patients with HBsAg levels below 1000 IU/mL whereas for Asian patients, withdrawal should only be considered when HBsAg levels get below 100 IU/mL.

One question that has arisen is whether ALT flares af-

ter NA withdrawal are required for HBsAg loss. While some studies have reported flares followed by HBsAg clearance, emerging data suggest that in most settings ALT flares are not likely to lead to HBsAg loss and may be harmful. In the Hepatitis B Research Network study, patients stopped tenofovir after 4 years of therapy. The study allowed participants to have significant hepatitis flares before restarting antiviral therapy. The results showed that in fact patients without flares had the greatest reductions in qHBsAg and were more likely to clear HBsAg. Indeed, the flares were not associated with HBsAg loss, at least in the 2 year follow-up of the study. Individuals who had a rise in HBV DNA above 4 log IU/mL were very likely to experience subsequent ALT flares and thus the authors suggested that this HBV DNA threshold should be considered as an indication to restart therapy to avoid ALT flares that are not helpful and may be harmful. Other studies have reported similar findings.

More recently, data evaluating other HBV biomarkers have suggested that both hepatitis B core- related antigen (HBcrAg) and HBV RNA may both be predictive of outcome. These markers are thought to reflect cccDNA transcriptional activity and a large retrospective study from Europe found that HBcrAg levels could add to the predictive ability of qHBsAg levels. Similarly, data from the HBRN withdrawal study suggested that if participants had detectable HBV RNA at the time of NA withdrawal, they were unlikely to benefit from withdrawal and more likely to go to active disease and require retreatment. While these markers are not currently available for clinical use, they may hold promise to more accurately risk stratify and identify patients likely to benefit from NA withdrawal.

Society guidelines differ somewhat in their approach to treatment withdrawal as a therapeutic approach, which likely reflects the evolving data in this field. One area of clear consensus is the need to be careful with NA withdrawal. To consider NA withdrawal, patients must be HBeAg- negative and ideally anti-HBe positive with undetectable HBV DNA and normal ALT. Although many patients with cirrhosis were stopped due to reimbursement criteria in Asia and not all ran into trouble, the presence of cirrhosis is clearly a risk factor for complications post-withdrawal and most would agree that those with cirrhosis (ever) should not discontinue therapy. In addition to these factors, it is critically important to ensure that patients who stop NA therapy are followed closely after stopping. The risk of severe hepatitis is real and hard to predict. If patients are unlikely to be adherent with close follow-up, treatment withdrawal should be avoided. While treatment withdrawal has some potential advantages, it is important to remember that the alternative approach of continuing NA therapy until HBsAg loss is very safe and the only downsides are the need for daily medication and its associated costs. Clearly there are pros and cons to both approaches, but evolving data will hopefully allow us to select

patients more accurately who are at low risk of harm and may benefit from NA withdrawal. Understanding these factors may also be important for interpreting data with new HBV curative regimens to accurately predict who can safely stop NA therapy after completion of new treatment regimens.

Application of Current Biomarkers to Guide Anti-HBV Treatment

Tetsuya Hosaka

Toranomon Hospital, Japan

Some serological hepatitis B virus (HBV) markers, such as hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and HBV DNA, are now available in the real-world clinical settings for chronic hepatitis B patients (CHB). HBV DNA is one of the most important markers for making a decision whether or not to start antiviral treatment (AVT) for CHB and is adopted along with ALT levels in some international guidelines.[1,2] However, a large population of patients falls outside the criteria for starting AVT, and are categorized as indeterminate phase, so called "Grey-Zone".[3,4] Recent study showed that patients categorized into such indeterminate phase had higher risk of HCC than those into inactive CHB.[5]

Hepatitis B core-related antigen (HBcrAg), which was developed in Japan, is a unique serological biomarker and reflects intrahepatic cccDNA and transcriptional activity of HBV.[6,7] We stratified the risk of HCC using this HBcrAg assay among HBeAg-negative patients with Grey-Zone. Cumulative HCC incidence rates in Grey-Zone patients with elevated HBcrAg had as high risks as those with immune-active CHB.[8] In this lecture, we will present the potential HBV markers including HBcrAg for the risk stratification of HCC and the guide of anti-HBV treatment.

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Can Antivirals Reduce Intrahepatic cccDNA and Integrate HBV DNA?

Marc G. Ghany

NIH, USA

Covalently closed circular (cccDNA) and integrated HBV DNA (iDNA) represent stable forms of HBV that contribute to viral persistence and difficulty in developing curative therapy. cccDNA is a stable replicative form of the viral DNA.[1] It resides in the hepatocyte nucleus as a non-integrated, episomal DNA (or mini chromosome) where it serves as the template for all the viral mRNAs and the pre-genomic RNA, which serves as the template for viral replication.[1] The copy number is estimated to be 1-5 copies per cell and its persistence after functional cure is the reason for HBV reactivation. The molecular mechanisms responsible for the conversion of rcDNA to cccDNA remain unclear. Based on the structure of the rcDNA certain key steps must include removal of the viral polymerase from rcDNA giving rise to a protein-free rcDNA as the precursor for cccDNA biosynthesis, removal of the RNA primer and the small redundancy r, filling in the gap in the positive strand and then ligation of the negative and positive strands.[1] Host and viral enzymes play a role in this process. Elimination of cccDNA may be through cytolytic and non-cytolytic mechanisms and through cell turnover. There is some controversy of how levels of cccDNA are maintained in the hepatocyte following its establishment. One model suggests that cccDNA levels are stable with minimal turnover whilst another model suggests the opposite, cccDNA undergoes constant degradation and replenishment to maintain copy numbers at an equilibrium.[2] Replenishment of cccDNA may occur by 2 routes: an intracellular recycling pathway of de-novo synthesized nucleocapsids or through reinfection of hepatocytes with new rounds of infection.[2]

Given its central role in HBV infection, elimination of cccDNA is the holy grail of HBV therapy. There is evidence that both the approved drugs for treatment of chronic hepatitis B (CHB) interferon (IFN) and nucleos(t)ide analogues (NA) influence cccDNA levels. Interferon-α was shown to reduce cccDNA levels by 80% after 10 days of treatment in-vitro.[3] Elegant mechanistic studies demonstrated that interferon-α and lymphotoxin-β-receptor activation mediate their effects on cccDNA via APOBEC3A and 3B-mediated deamination of the (-)-strand and subsequent degradation of cccDNA.[3] Several studies using different NAs have reported decline of cccDNA levels.[4-7] The mean decline after 48 weeks of therapy is ~1 log. The addition of pegIFN to a NA results in greater decline in cccDNA ~1-2.4 log and extending the duration of therapy may lead to a higher decline in cccDNA levels to ~3 log. NAs are postulated to reduce cccDNA by lowering viral load and therefore infection of uninfected hepatocytes. Many other strategies are being pursued to target cccDNA. One approach is to target cccDNA production by blocking host factors involved in the multiple steps of RC-DNA to cccDNA conversion. Another is to prevent nuclear import of RC-DNA by capsid-targeting drugs. Thus far such a strategy has been ineffective. Presence of RC-DNA in the cytoplasm may trigger DNA sensors like cyclic GMP-AMP synthase (cGAS) and activate STING to in-

duce antiviral cytokines to eliminate cccDNA. Silencing of cccDNA transcriptional activity by inducing the host cell's epigenetic machinery, or by blocking the de-silencing activity of HBV X protein. Degradation of existing cccDNA by immune-mediated mechanisms, via APOBEC enzymes, or by directly cleaving cccDNA using genome editing with designer nucleases such as zinc finger nucleases, transcription activator-like effector nuclease (TALEN) and CRISPR/cas9 are other novel approaches.

Uncommonly, during replication of the viral genome there is a failure of the RNA primer to switch templates leads to priming originating from the DR1 region giving rise to double stranded linear DNA (dslDNA) synthesis instead of rcDNA.[8] The resulting dslDNA can have several fates. It can serve as a template for cccDNA (but cannot generate double stranded DNA), it may become enveloped and circulate as virions and finally, be integrated. iDNA can occur throughout the host genome at sites of DS DNA breaks through non-homologous end joining or microhomology-mediated end joining. No specific chromosomal hotspot has been identified. In one study, the mean frequency of total integrations ranged from 1.5-5 x10^9 per 5 x 10^{11} hepatocytes and were not different among HBV phases.[9] Another study reported that iDNA was more frequent among HBeAg positive compared to HBeAg negative patients. Integration is an early event following infection and occurs throughout all phases of infection. All open reading frames (ORFs) may remain intact but only HBsAg and HBX ORFs remain under their native promoters and may be produced. iDNA cannot transcribe precore mRNA and pgRNA due to the loss of upstream basal core promoter and therefore cannot support viral replication.

An important question is whether antiviral therapy by inhibiting viral replication could reduce iDNA. Data from the TORCH study was designed to investigate the benefit of TDF to reduced liver disease progression in grey zone patients with mild HBV DNA and ALT elevations. iDNA was analyzed in paired liver biopsies performed pre- and end-of-treatment. At baseline the level of viremia was significantly correlated with the number of distinct viral integrations in both groups. At year 3, the correlation remained strong and significant in the placebo group but became weak and nonsignificant in the TDF group. Moreover, TDF compared to placebo achieved a significantly greater reduction in distinct viral integrations, with a 3.28-fold vs. 1.81-fold decrease, respectively, in the expressed integration per million reads.[10] Another study also investigated the effect of NA treatment on iDNA and hepatocyte clonal expansion. All patients had detectable iDNA at baseline, with a median integration frequency of 1.01 $\times 10^9$ per liver and hepatocyte clone size of 2.41 $\times 10^5$. After 1 year of treatment, HBV integration was still detectable in all patients, with a median of 5.74 $\times 10^8$ integrations per liver representing a 0.22 log reduction; and hepatocyte clone size of 1.22 $\times 10^5$ (a 0.40 log reduction).[11] From baseline through year 1 to year 10, there was a decreasing trend in both integration frequency and hepatocyte clone size.

In summary, current therapy reduces but does not eliminate cccDNA or iDNA. Many technical and biological challenges remain to eliminate cccDNA and iDNA. In the interim, achieving functional cure defined as HBsAg loss with or without anti-HBs and unquantifiable HBV DNA 24 weeks off therapy is an important clinical endpoint that is associated with improved clinical outcomes.

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Risk of HCC and Biomarkers after a Cure of Hepatitis B

Jeong Won Jang

The Catholic Univ. of Korea, Korea

Hepatocellular carcinoma (HCC) is a major global health concern, with chronic hepatitis B virus (HBV) infection being one of its leading causes. While antiviral therapies have made significant strides in controlling HBV replication and achieving viral suppression, it is very difficult to achieve HBsAg seroclearance, a functional cure of chronic HBV infection. HBsAg seroclearance is regarded as the most critical treatment endpoint of CHB. A reduction in HBV DNA and immune activity in patients achieving HBsAg seroclearance may, in general, result in improvement in histological hepatic damage, reduce HCC development and prolong survival.

However, despite the achievement of HBsAg seroclearance, intrahepatic HBV DNA and covalently closed circular DNA (cccDNA) may still persist in the liver. The intrahepatic HBV reservoirs can eventually induce hepatocarcinogenesis through the production of oncoproteins and HBV DNA integration into the host genome in some of the patients.

The reported annual incidence of HCC is 0.38% to 1.29% among patients who achieve HBsAg seroclearance. The studies showed several clinical factors for HCC development after a cure of hepatitis B, including underlying cirrhosis and old age (>50 year) at the time of HBsAg seroclearance, male sex, alcohol consumption, family history of HCC, and dual infection with HCV or HDV. As a functional cure of chronic HJBV infection is a rare event, the long-term course and prognostic factors after HBsAg seroclearance remain to be evaluated further.

This lecture will summarize published studies on a functional cure of hepatitis B and risk of HCC after HBsAg seroclearance as a cure of chronic HBV infection. It will also introduce an emerging field of biomarkers for HCC risk assessment and discuss the utility of serum biomarkers, such as alpha-fetoprotein (AFP), des-gamma-carboxyprothrombin (DCP), and other newer markers in monitoring individuals post-HBV cure. A comprehensive understanding of these dynamics is crucial for healthcare professionals, researchers, and policymakers in the ongoing battle against HCC in the post-HBV cure era.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 1 | Thursday, Sept. 21, 2023

PG Course 2. Treatment of Viral Hepatitis, What Progress Being Made?

Chairs:

Raymond T. Chung (Harvard Univ., USA)
Ming-Lung Yu (National Sun Yat-sen Univ., Taiwan)
Jin Mo Yang (The Catholic Univ. of Korea, Korea)

Current Optimal Treatment for Chronic HCV Infection in Various Clinical Situations

Jung Il Lee

Yonsei Univ., Korea

Currently available pan-genotypic HCV drug regimens such as sofosbuvir/velpatasvir and glencaprevir/pibrentasvir theoretically enable treatment without identifying HCV genotypes and subtypes. Moreover, in order to increase the global infection cure rates in any setting where genotype and subtype determination is not available or not affordable, simplified, genotyping-free pangenotypic HCV treatment has been recommended. However, in the regions where HCV genotype and subtype determination are available and affordable so as not to limit access to care, the information on HCV genotype/subtype remains useful to optimize the result of HCV treatment. In addition, some distinct subtypes of genotypes 1 to 8 have been shown to be highly prevalent that show natural polymorphism that confer inherent resistance to NS5A inhibitors resulting in unacceptably high virological failures.[1-5] Therefore it is still useful to determine the HCV genotype and subtype unless in the regions where assessing genotype might limit access to care.

For the initial treatment in those without liver cirrhosis or with compensated liver cirrhosis Interferon-free, ribavirin-free DAA-based regimens are preferred due to the virological efficacy, ease of use, safety and tolerability.[6]

Regimen	Genotype	Duration
Treatment-naïve without cirrhosis or with compensated cirrhosis		
Glencaprevir/pibrentasvir	1-6	8 weeks
Sofosbuvir/velpatasvir	1-6	12 weeks
Ledipasvir/sofosbuvir	1,4,5,6	12 weeks
	1 without cirrhosis	8 weeks
Elbasvir/grazoprevir	1b, 4	12 weeks

Patients with decompensated cirrhosis (Child-Pugh B or C) and those with compensated cirrhosis (Child-Pugh A) with prior episodes of decompensation should be considered similarly. In these patients, DAA-based regimens are the most suitable treatment options, although the protease inhibitors should not be used due to substantially higher drug exposure and risk of toxicity.[7] In the ASTRAL-4 study, patients with Child-Pugh B cirrhosis infected with genotype 1 to 4 were randomized to receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, for 12 weeks with weight-based dosed ribavirin or for 24 weeks without ribavirin.[8]The SVR12 rates, respectively, were: 89% (16/18), 100% (14/14), and 87% (14/16) in patients with genotype 1b infection: 100% (4/4), 100% (4/4) and 75% (3/4) in patients with genotype 2 infection.[8] In the SOLAR-1 study, patients with Child-Pugh B cirrhosis infected with genotype 1 and 4, were randomized to receive the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with weight-based dosed ribavirin or for 24 weeks with ribavirin.[9] Of those, 10 genotype 1b patients were included in 12 week treatment regimen and 7 patients were included in 24 week regimen. The SVR 12 rates were 87% (26/30) and 89% (24/27), respectively. In the SOLAR-1 study, 49 Child-Pugh C patients without liver transplantation were also treated with either 12 or 24 weeks of sofosbuvir/ledipasvir and ribavirin. In the group, 6 genotype 1b patients were included in 12-week regimen and 8 patients were in 24-week regimen. The SVR rates were

86%(12/22) and 87%(20/23), respectively.

Regimen	Genotype	Duration
Treatment-naïve with decompensated cirrhosis		
Sofosbuvir/velpatasvir with weight-based ribavirin	1-6	12 weeks
Sofosbuvir/velpatasvir	1-6	24 weeks
Ledipasvir/sofosbuvir with weight-based ribavirin	1,4,5,6	12 weeks
Ledipasvir/sofosbuvir	1,4,5,6	24 weeks

Genotype 1b or 2 patients who have experienced treatment failure with a sofosbuvir-based regimen should be retreated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir.[10-12] Glecaprevir/pibrentasvir for 16 weeks can be used as an alternative retreatment regimen.[13-15] . For genotype 1b or 2 patients without liver cirrhosis or with compensated liver cirrhosis with prior glencaprevir/pibrentasvir treatment failure can be retreated with glencaprevir/pibrentasvir plus ribavirin and sofosbuvir.[16] These patients can also be treated with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks.[17]

Conventionally, HCV infection has been classified either acute hepatitis C, defined as the first 6 months of infection, or chronic infection which follows after acute stage of the infection which lacks spontaneous clearance. Since acute hepatitis C is often asymptomatic,[18] the establishment of precise time of infection is challenging. It is very well known that certain proportion of acute hepatitis C infection may result in spontaneous clearance, and several funding authorities, including the Korean government have refused treatment reimbursement in patients considered to have acute hepatitis C. However, recent data demonstrate that DAA treatment in the early phase of HCV infection is cost-effective whereas postponing therapy to meet the criteria for chronic infection increases the risk of HCV transmission.[19] Moreover, a study with HIV-infected patients, the lack of 2-log drop of HCV RNA levels 4 weeks after the initial presentation predicts a low-likelihood of spontaneous clearance (negative predictive value less than 1%).[6] Given the high efficacy and safety of current HCV DAAs, delaying the treatment might be a barrier to HCV elimination.

Studies reported lower SVR rates in HCC patients treated with various DAA regiments[20] and higher SVR rates were shown in those who received curative HCC treatment.[21] Therefore it has been recommended that HCV patients without liver cirrhosis or with compensated liver cirrhosis whose HCC can be curatively treated (liver resection, ablation or transplantation) have HCV treatment deferred until after complete HCC treatment.[22] In addition, a retrospective US cohort study including HCV-related HCC patients who achieved a complete response to not only resection, ablation therapy but also trans-arterial chemo/ratio-embolization, and radiation therapy has shown that DAA treatment of HCV infection was associated with a significant increase in survival rates.[23] There are several evidences showing that DAA-induced SVR is associated with a significant reduction in the occurrence of de novo HCC, and in mortality rates.[20,24,25] However, the presence of active HCC is associated with significant decrease in SVR rates after DAA treatment.[22] Although this is still under debates, it has been recommended that DAA therapy can be deferred 4-6 months in patients without liver cirrhosis or Child-Pugh A compensated cirrhosis to assess HCC treatment response.

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Strategies for the Elimination of Hepatitis C

Norah Terrault

Univ. of Southern California, USA

An estimated 58 million individuals are infected with hepatitis C virus (HCV) and annually ~700,000 deaths occur. Southeast Asia and Asia-Pacific regions account for about 40% of the global infection burden. A recent update on global progress on HCV elimination was discouragingly, with more than 75% of viremic persons still undiagnosed and less than 10% of the global population treated. While the pandemic was responsible for interruptions in elimination efforts, the scale up on testing, surveillance and vaccination for COVID-19 provide an opportunity to leverage that infrastructure to accelerate HCV testing, surveillance, and treatment. Simplification of diagnosis and treatment is possible, enabling non-specialists to deliver HCV care. Persistent barriers to screening and treatment include a lack of awareness by patients and providers, with stigmatization also contributing to lack of engagement. Regional and national campaigns to normalize the need for testing coupled with prevention messages could help to overcome this barrier and aid in preventing new infections. The colocalization of diagnosis and treatment yields the highest success in completing the cascade of care – so a test-and treat approach is advocated. For this approach to work, point-of-care tests that can establish presence of viremia with high certainty (such as with HCV core antigen or point-of-care HCV RNA tests) are needed. Accelerated approval pathways for point-of-care diagnostics and low-cost diagnostics are important for global elimination efforts. Additionally, there remain barriers to accessing the direct-acting antivirals, largely due to their cost. This barrier has been reduced with availability of generics and the ability of national programs to negotiate lower drug costs. Finally, recognizing that a high burden of infection lies among those who use drugs, incarcerated persons, and among immigrant populations a comprehensive approach to care is best, addressing mental health and addiction as well as urgent social needs (homelessness). Models of care that bring diagnosis and treatment to HCV "to the patient wherever they are" are increasingly the focus of elimination efforts.

Current and Emerging Therapeutic Approaches to HDV Infection

Maria Buti Ferret

Hospital Universitario Valle Hebron, Spain

Hepatitis D virus (HDV) or hepatitis delta virus, is the smallest virus capable of causing human disease. It is unable to replicate on its own and can only propagate in the presence of hepatitis B virus (HBV). Hepatitis D Infection is the most severe viral hepatitis, with the highest instances of cirrhosis, liver failure and hepatocellular carcinoma (HCC) at younger ages. Pegylated interferon-alpha (Peg-IFN-alpha) is the primary drug of choice for the treatment of HDV. IFN-alpha is a type I interferon, widely used to treat many viral infections because of its beneficial antiviral. Peg-IFN has been mainly used for treatment although has never received the approval for regulatory agencies. The treatment duration is usually at least 1 year, and response rates are approximately 20% to 30%, with a high rate of posttreatment relapse. In addition, the side effects of interferon α are considerable, typically including flu-like symptoms, myalgias, headaches, depression, and cytopenias, which can be very significant. Prolonged therapy may require dose reduction. Thus, there is a need for effective treatment for HDV.

Bulevertide , an Virus entry inhibitor has received approval by the European Medicines Agency. It is a subcutaneous drug that appears to be safe. Its antiviral efficacy increases with treatment duration. IN the phase 3 clinical trial, after 48 weeks of bulevirtide treatment, HDV RNA and ALT levels were reduced in patients with chronic hepatitis D. Combining bulevirtide with pegIFN has the highest antiviral efficacy short-term, but its use is limited by pegIFN. Prenylation inhibitor lonafarnib and pegIFN lambda are in phase 3 and nucleic acid polymers in phase 2 of drug development. Nucleic acid polymer, drugs under evaluation for Chronic hepatitis B has also been studied for Hepatitis D. These compounds led to HBsAg clearance in a sizable proportion of patients. PegIFN lambda seems to be associated with less IFN typical side effects and currently is in phase 3.

HBV-HCV Dual Infection: Changing Epidemiology and Treatment in Asia

Chun-Jen Liu

National Taiwan Univ., Taiwan

We may encounter patients with hepatitis C virus (HCV) and hepatitis B virus (HBV) coinfection in HBV or HCV endemic areas. Coinfection can also be found in populations at risk for parenteral transmission. Community cohort and hospital-based case-controlled studies have demonstrated a higher risk of liver disease progression in those with HCV/HBV coinfection in comparison with HBV or HCV mono-infected patients. Fortunately, the rate of HCV/HBV coinfection has been shown to be declining after the launch of HBV vaccination program in high-risk populations. Earlier trials supported the value of combination therapy of peginterferon alfa-2a or -2b and ribavirin for co-infected patients with positive HCV RNA. Furthermore, HBsAg seroclearance can be achieved in about 30% of the co-infected patients within 5 years after initiating peginterferon-based therapy. However, there still exist unmet needs for those coinfected patients who are unable to tolerate or are ineligible for peginterferon-based therapy. The advent of new direct-acting antivirals (DAAs)-based anti-HCV therapy increases the rate of HCV clearance and fills the unmet gap for such patients. A recent multicenter trial in Taiwan demonstrated that the HCV sustained virologic response rate was high (100%) in coinfected patients with genotype 1 or 2 infection. Notably, DAA would not have any activity against HBV infection; thus, may therefore HBV reactivation and related hepatitis activity while on HCV therapy or after cure of HCV as warned by the US FDA. Our trial data demonstrated that ~70% of the subjects experienced HBV reactivation event within 48 weeks after start of DAA therapy. HBV reactivation can be successfully prevented through simultaneous usage of anti-HBV agents. Overall, major advances in the management of HCV/HBV coinfection including prevention of HBV reactivation have been made over the past 20 years.

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APASL STC 2023 BUSAN

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"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 1 | Thursday, Sept. 21, 2023

Joint Symposium (East Asia): HCV Elimination

Chairs:

Lai Wei (Tsinghua Univ., China)
Masao Omata (The Univ. of Tokyo, Japan)
Sook-Hyang Jeong (Seoul National Univ., Korea)

Cost-Effectiveness of HCV Screening in Korea: A Step towards HCV Elimination

Sook-Hyang Jeong

Seoul National Univ., Korea

There are many challenges to eliminating hepatitis C virus (HCV) infection by 2030 in South Korea, which include a low rate of awareness, no effective national screening strategy, low rate of linkage of care, and high cost of direct-acting antivirals (DAA) therapy.

National Health Insurance of South Korea provides and pays for the essential items of health examination (National Health Examination, NHE) according to the age of the population. More than 75% of the total population voluntarily received NHE, so it is a very powerful system for early detection of HCV infection for the general population. Therefore, we conducted studies to evaluate the cost-effectiveness of HCV screening using the NHE program compared to no screening in a targeted population aged 45-65 years from societal and healthcare system perspectives in Korea, where anti-HCV prevalence is 0.6%.

A decision tree and Markov model were established and used to compare the expected costs and quality-adjusted life years (QALY) between one-time screening and no screening strategy. The population aged 40-65 years was simulated in a model spanning a lifetime from both the healthcare system and societal perspectives. The incremental cost-effectiveness ratio (ICER) between targeted population screening and no screening was estimated.

Our first study published in 2019 and updated in 2022 both showed that the ICERs of the screening strategy were far less than the willingness-to-pay threshold of 25,000 USD. It means that the targeted population screening would be highly cost-effective from both the healthcare system and societal perspectives. In various sensitivity analyses, the most influential parameters on cost-effectiveness were anti-HCV or HCV RNA prevalence, screening test costs, and treatment acceptance rate. However, all ICERS in the sensitivity analysis were consistently less than the threshold. Moreover, another 2 studies conducted by other investigators on this subject also showed that similar screening strategies were highly cost-effective.

In conclusion, one-time targeted population screening in the Korean population aged 40-65 years using the NHE program would be highly cost-effective from both the healthcare system and societal perspective.

Clinical Challenges in HCV Management in Japan

Atsumasa Komori

Nagasaki Univ., Japan

The global hepatitis strategy of WHO aims to reduce new hepatitis infections by 90% and mortality by 65%, from baseline 2016 to target 2030. Alongside and even beforehand, the Ministry of Health, Labor and Welfare (MHLW) of Japan introduced several cornerstone public health policies for reducing the burden of viral hepatitis.[1,2] First of all, 5-year project for the national screening of HBV and HCV among all residents at and over 40 years old was implemented in 2002 and are continuing with their success. The screening strategy for HCV uses the combination of anti-HCV measurement and HCV RNA detection using NAT at the same time, to survey asymptomatic cases in the general population. Secondly, the regional core specialty hospitals for liver disease were established in all prefectures of Japan in 2007 under the notification of the Health Bureau of the MHLW, in order to improve the patient care service for viral hepatitis. Thirdly, the medical expense subsidy system was installed in 2008, and finally the Basic Act on Hepatitis Measures has been formulated thereafter since 2010.

What are the consequences of the policy for chronic HCV infection in Japan, with regard to action goals in the WHO agenda? First, according to the registry of acute liver hepatitis by NHO liver study group, being comprised of 35 hospitals around Japan, the annual incidence of acute HCV infection was dropped steeply from 2014, when DAA became widely available under the subsidy system for the treatment of chronic HCV infection (Yamasaki K, personal communication). Second, the incident cases of HCV-associated hepatocellular carcinoma (HCC), a surrogate for the mortality associating with HCV, which was surveyed by the Liver Cancer Study Group of Kyushu, tended to decrease between quarters during 1996 and 2019; in the last quarter, the prevalence of non-HBV/HCV HCC outcompeted that of HCV-HCC (45.6 % vs 40.4 %).[3]

Despite the above progress, there are still unmet needs and challenges towards 2023 goal in Japan. To eliminate acute infection at near 100 %, socioeconomic disparity should also be taken into account, regarding the treatment of the highest-risk population, including people who inject drugs and those incarnated in prisons.[4] Additionally, appropriate and standardized screening strategy for the post SVR HCC should be implemented, in particular among those with advance stage of fibrosis, with sufficient two-way communication between medical professions and patients. Regional core specialty hospitals could still contribute substantially for such provision.

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How Would China Achieve WHO's Target of Eliminating HCV by 2030?

Lai Wei

Tsinghua Univ., China

Chronic hepatitis C (CHC) is an escalating global health concern, and is one of the leading causes of cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality.1-3 Worldwide, China has the greatest number of patients with hepatitis C virus (HCV) infection in the world, accounts for more than 14% of the global CHC prevalence. Moreover, almost a fifth of the total annual deaths from HCV-related cirrhosis and HCC occur in China.

In 2016, the World Health Organisation (WHO) introduced its first global strategy to eliminate viral hepatitis as a public health threat by 2030. However, in 2016, it was estimated that only 18% of the HCV-infected population in China has been diagnosed and although 25% of the 10 million CHC patients required urgent treatment, fewer than 1.3% actually received treatment.

Government led by Ministry of Health released call to eliminate the threat of HCV infection in China in August, 2021, since then, local government from 29 province have been starting actions, including screen in hospital, blood station, linkage from CDC to hospital, and DAAs reimburse policy.

Some special populations were select as micro-elimination population. With the registers of the Dynamic Management and Control System for Illicit Drug Users, IDUs were be identified and targeted as micro-elimination in a few of provinces. Meanwhile, dialysis populations is under and will be another micro-elimination population in Hubei, Yunnan, Guangxi, Hunan and Xinjiang provinces. HIV co- infection was integrated with HCV infection screen and as one of micro- elimination population.

Linkage-to-Care and Follow-Up Strategy for HCV Infection in Taiwan

Tai-Chung Tseng

National Taiwan Univ., Taiwan

Hepatitis C virus (HCV) infection remains a substantial health burden in Taiwan. Achieving the World Health Organization's (WHO) goal of eliminating viral hepatitis by 2030 requires innovative and targeted strategies to ensure linkage to care as direct-acting antivirals (DAAs) is so effective and tolerable for HCV cure. An example of Taiwan's success is the HCV elimination efforts in Changhua county. The local government adopted a top-down strategy and achieved a great success in the targeted elimination of HCV within a subgroup of 10,848 patients with type 2 diabetes mellitus (DM). This subgroup exhibited a notably higher prevalence of chronic HCV infection. To address this issue, a comprehensive shared care network was established, connecting over 80% of hospital-based diabetes clinics and relevant primary care facilities throughout the county. This initiative integrated an all-in-one HCV care cascade into the diabetes care framework, optimizing the structure of care delivery. This approach eliminated the need for extra patient visits, duplicated blood draws, and redundant procedures. As a direct outcome of these improvements, the cumulative treatment coverage underwent a remarkable surge, escalating from a 4.65% to an impressive 73.78%. Another notable success story stems from Kaohsiung, where a micro-elimination strategy was executed to combat HCV infection in patients undergoing hemodialysis. Employing a multifaceted approach, including outreach efforts, mass screenings, and group treatment conducted on-site, HCV micro-elimination among the hemodialysis population was significantly facilitated. Among the cohort of 2,323 uremic patients, 178 (7.7%) were identified as HCV-viremic. Remarkably, 83.9% of these patients received DAA treatment, with nearly 90% of sustained virological response using per-protocol analysis. These two distinct examples exemplify Taiwan's dedication to addressing HCV infection through innovative strategies. The collaborative initiatives in Changhua county and the focused efforts in Kaohsiung city underscore the potential for targeted interventions to yield substantial impact in the quest for global HCV elimination.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 1 | Thursday, Sept. 21, 2023

Symposium 1-2. Immunology and Immunotherapy of Viral Hepatitis

Chairs:

Hideki Ueno (Kyoto Univ., Japan)

Eui-Cheol Shin (KAIST, Korea)

Immunological Profile of Chronic HBV Infection: Can It Help to Improve Therapeutic Success?

Antonio Bertoletti

Duke-NUS Medical School, Singapore

A coordinated HBV-specific humoral and cellular immune response is linked with a rapid HBV control, while a defect of the antiviral immune response defines chronic HBV infection (CHB).

Different therapies aiming to activate directly or indirectly the antiviral immunity of CHB patients have been therefore developed and tested to overcome such defects. Unfortunately, the clinical results have been so far not optimal, since functional HBV cure is still achieved in a minority of treated patients. A testable hypothesis is that the clinical success of different CHB therapeutic strategies can be augmented by developing more precise criteria for patient selection. CHB patients have been traditionally categorized based on virological (HBeAg+ or negative, HBV-DNA) and liver inflammatory parameters (presence or absence of transaminases), while the heterogeneity of the immunological defects present in the broad population of patients with CHB has been systematically ignored. I will discuss how the development of widely applicable, point-of-care immunological tests might allow a more accessible measurement of immunological parameters in patients with CHB that can permit better patient selection.

Immunological Scar after HCV Clearance

Eui-Cheol Shin

KAIST, Korea

Patients with chronic hepatitis C virus (HCV) infection exhibit abnormal alternations of several immunological features, which are not normalized after viral elimination by direct-acting antiviral (DAA) treatment. For example, mucosal-associated invariant T (MAIT) cells exhibit a reduced frequency and decreased IFN-γ production, which are sustained after HCV clearance by DAA treatment.[1] Furthermore, successful viral clearance by DAA treatment does not lead to restoration of the impaired proliferation and effector function of HCV-specific $CD8^+$ T cells, i.e., $CD8^+$ T cells retain features of exhaustion.[2-5] Epigenetic studies have also demonstrated sustained exhaustion of HCV-specific T cells,[6,7] revealing an epigenetic scar of sustainedly increased chromatin accessibility in exhaustion-related genes. In addition, we recently found that the peripheral blood $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cell population is expanded during chronic HCV infection, and this expansion is sustained after viral clearance. Further studies are warranted to examine the clinical significance of sustained immunological alterations after recovery from chronic HCV infection.[8]

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T-Cell Responses against Human Coronaviruses in Human Liver

Hideki Ueno

Kyoto Univ., Japan

Several human viruses, such as HAV, HBV, and HCV, exhibit hepatotropism. Infection by these viruses elicits specific T-cell responses within the liver tissue. Following the resolution of acute infections, some antigen-specific T cells persist within the tissue as long-term liver-resident memory cells, playing a protective role against reinfection. In the case of chronic infections caused by HBV and HCV, viral antigen-specific T cells also persist in the liver tissue but often become exhausted, leading to a loss of functionality. Moreover, apart from hepatotropic viruses, the liver also hosts T cells that target other viruses, including EBV, CMV, and Flu. When the liver encounters hepatotropic viral infections, these T cells can become activated by inflammatory cytokines, regardless of their specificity, potentially causing hepatitis and liver damage.

Therefore, the human liver harbors T cells with diverse antigen-specificities and biological states, but our understanding of their biological characteristics remains limited. In my talk, I present our approach for analyzing liver-resident antigen-specific T cells using liver perfusate. By culturing liver perfusate with recombinant viral antigens for 24 hours and subsequently analyzing the activated T cell population through flow cytometry (FCM), we were able to characterize liver-resident antigen-specific T cells. Applying this method, we found that the human liver contains SARS-CoV-2 S protein reactive cells. The composition of SARS-CoV-2-reactive T cell subsets differed between liver-resident and circulating blood T cells, with a higher frequency of regulatory T cells present in the liver. This finding suggests that a fraction of liver-resident T cells maintain a regulatory status to suppress the activity of their inflammatory counterparts.

Novel Immunological Therapeutics for Cure of HBV Infection

Wonseok Kang

Sungkyunkwan Univ., Korea

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

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DAY 1 | Thursday, Sept. 21, 2023

Symposium 1-3. Emerging Antivirals for HBV Cure

Chairs:

Jidong Jia (Capital Medical Univ., China)

Seong Gyu Hwang (CHA Univ., Korea)

Updates on Drugs for HBV Entry and Post-Entry Inhibition

Hyung Joon Yim

Korea Univ., Korea

Antiviral drugs are being developed focusing on inhibition of viral life cycles. Entry inhibitors are a class of antiviral drugs that target the initial steps of the hepatitis B virus (HBV) life cycle by preventing the virus from entering hepatocytes. Entry inhibitors offer a different mechanism of action compared to traditional antiviral drugs used to treat chronic HBV infection. By targeting the initial step of the viral life cycle – viral entry – these inhibitors have the potential to reduce viral load, prevent infection of new cells, and inhibit the spread of the virus.[1]

Myrcludex B (Bulevirtide) is a promising entry inhibitor that targets the sodium taurocholate co-transporting polypeptide (NTCP) receptor on liver cells, which HBV uses to enter and infect cells.[1] By blocking this receptor, Myrcludex B prevents the virus from gaining entry. It has shown effectiveness in reducing viral load and liver inflammation in the recent clinical studies involving patients with chronic hepatitis B and D coinfection.[1,2]

Cyclosporin A showed HBV entry inhibitory activity at a micromolar range from drug screenings.[3] It was reported that cyclosporine A interrupts the attachment of HBV by binding to the site of NTCP where interaction with the PreS1 domain of HBV occurs.[3] SCY-446 and SCY450 are cyclosporine derivatives without immune suppressive effects.[4] These are cyclophilin inhibitors that could potentially inhibit HBV entry as cyclophilins are cellular proteins that play a role in the viral entry process. In addition, SCY-446 and SCY450 showed no decrease in NTCP transporter activity, resulting in minimizing side effects.

Several clinical available small molecules also exhibit inhibitory activity against HBV entry into hepatocytes.[5] These include rosiglitazone, zafirlukast, sulfasalazine, and etc. Whether these molecules can be repurposed to anti-HBV drugs seems to be of interest.

While entry inhibitors are a significant avenue of research, a complete cure for chronic HBV infection is not attainable through this single approach. HBV establishes a stable covalently closed circular DNA (cccDNA) form in hepatocytes, which is not effectively targeted by current antiviral drugs, including entry inhibitors. Achieving a cure for HBV may involve a combination of therapies aimed at eliminating or reducing cccDNA along with suppressing viral entry and replication.

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Updates on HBV Capsid Assembly Inhibitors

Robert G. Gish

Hepatitis B Foundation, USA

Currently approved treatments for patients with chronic hepatitis B virus (HBV) infection rarely achieve a functional cure. Numerous new compounds are identified, including capsid assembly modulators (CpAMs/CAMs). CAMs interfere with viral pre-genomic RNA (pgRNA) encapsidation and are effective in viral load reduction but have limited effects on hepatitis B surface antigen (HBsAg). There are proposed effects of CAMs on covalently closed circular DNA (cccDNA) replenishment and may result in long-term viral suppression of therapy if this is proven in human clinical trials.

Key points:

- Current therapy is insufficient to induce functional cure, defined as HBsAg seroclearance, among patients with chronic hepatitis B (CHB) infection.
- CAMs are a new type of virus-directed therapy, among many others, which are being evaluated in clinical trials aiming to enhance functional cure in subjects with CHB infection.
- CAMs act by formation of aberrant capsids or empty capsids, thereby prohibiting encapsidation of pgRNA.
- There are 2 forms of CAMs: empty particles and a dysmorphic form that is dysfunctional.
- CAMs (oral administration) are potent in suppressing viral nucleic acids but have demonstrated minimal effect on HBsAg levels.

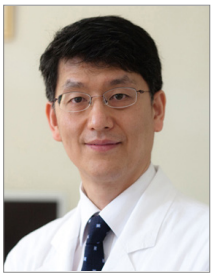
There is great excitement as third-generation CAMs move forward to phase II and III trials with a recent study from Aligos Therapeutics showing HBsAg loss for the first time in human trials. These third-generation CAMs have picomolar concentrations, resulting in effect at viral reduction at a low EC50 with no initial signs of resistance.

Updates on Drugs Targeting HBV RNAs: ASOs and siRNA

Jidong Jia

Capital Medical Univ., China

Among the novel approaches to directly inhibit the hepatitis B virus (HBV) life cycle, therapies based on RNA interfering technology have been extensively studies in clinical trials. As two basic types of RNA interfering, small interference RNAs (siRNAs) lead to mRNA degradation via RNA-induced silencing complex (RISC) and antisense oligonucleotides (ASOs) lead to mRNA degradation via activation of RNaseH. Many clinical trials have been registered at the clinicaltrial.gov but some have already stopped further developing due to various reasons including efficacy, safety, or commercial considerations. The next are just some examples of clinical trials reported in literature or at the recent international liver conferences. VIR-2218 is a GalNac-conjugated pangenotypic siRNA. In a Phase II clinical trial, two monthly doses of VIR-2218 to 24 patients with NUC suppressed CHB resulted in a 1-log HBsAg decline that maintained for 28 wk after treatment in some patients, supporting further clinical trials on therapeutic effect of VIR-2218. Preliminary results showed that combining pegylated interferon further improved the efficacy of VIR-2218. Bepirovirsen (GSK3228836) is an ASO without GalNac conjugation that targets all four ORFs of HBV by binding to the complementary mRNAs. The published phase 2a and 2b (B-Clear) results showed that multiple doses of bepirovirsen resulted in a significant reduction in or even loss of HBsAg in patients with or without previous NUC therapy. The simultaneous suppression of HBcAg and HBV RNA suggests a remarkable down-regulation of cccDNA transcriptional activity. Further on-going clinical trials on this agent includes intrahepatic immunology(B-Fine), combination therapy with pegylated interferon, (Be-Together) and durability study after stopping all the medications (B-Sure). In addition, combining therapy with agents of different class may improve the efficacy.



Updates on cccDNA Disruptors

Jin-Wook Kim

Seoul National Univ., Korea

Since the introduction of potent nucleos(t)ide analogue, novel therapeutic strategies are being pursued for the cure of chronic hepatitis B virus (HBV) infection. Because replication of HBV depends on the presence of covalently closed circular DNA (cccDNA) in hepatocytes, genome editing technologies are being tried to target HBV cccDNA[1]. Programmable nucleases, such as clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have site-specific targeting activities and near / in clinical trials[2,3]. ZFNs and TALENs have been shown to suppress HBV in vitro / in vivo[4,5], but CRISPR/Cas9 has been most actively investigated and proof-of-concept studies revealed encouraging results[6,7]. Off-target effects and efficiency of gene delivery system are main hurdles for the clinical use of gene editing strategy against HBV cccDNA.

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SIG 1. Diagnostic and Therapeutic Targets for Virus-Associated HCC

Chairs:

Chul Ju Han (Korea Cancer Center Hospital, Korea)
Won Young Tak (Kyungpook National Univ., Korea)

Novel Blood-Based Biomarkers for Diagnosis of HCC in Chronic Viral Hepatitis

Jaeyoun Cheong

Ajou Univ., Korea

Hepatocellular Carcinoma (HCC) stands as one of the leading causes of cancer-related mortality worldwide, particularly in the context of chronic viral hepatitis. Timely and accurate diagnosis of HCC is crucial for enabling effective therapeutic interventions and improving patient outcomes. Conventional methods, such as imaging techniques and alpha-fetoprotein (AFP) measurement, suffer from limitations related to sensitivity, specificity, and early-stage detection. These challenges have fueled the search for novel blood-based biomarkers that can complement or enhance the existing diagnostic armamentarium. The emergence of blood-based biomarkers has shown promising potential in revolutionizing HCC diagnosis, offering non-invasive, cost-effective, and reproducible alternatives to traditional methods.

The exploration of genetic, epigenetic, proteomic, and metabolomic alterations associated with HCC has led to the identification of a multitude of potential blood-based biomarkers. Notable examples include circulating nucleic acids [circulating tumor DNA, circulating tumor RNA (microRNAs, lncRNA etc)], proteins (cytokeratin 19, golgi protein 73, alpha-L-fucosidase, glypican-3 etc), exosomes (exosomal lipid and proteins, exosomal nucleic acids) and circulating tumor cells. These markers exhibit promising sensitivity and specificity profiles in various stages of HCC, providing valuable insights into both early and late-stage detection. Recent studies demonstrate that leveraging machine learning algorithms and multiplexed assays further enhances the discriminatory power of these markers. Moreover, the non-invasive nature of blood-based tests improves patient compliance, enabling regular monitoring and early intervention.

Despite their potential, blood-based biomarkers face challenges related to standardization, validation across diverse populations, and integration into clinical practice. Ongoing research aims to address these issues and establish guidelines for optimal utilization of these markers in routine clinical settings.

The exploration of novel blood-based biomarkers presents a paradigm shift in the diagnosis of HCC in the context of chronic viral hepatitis. These markers offer enhanced diagnostic accuracy, convenience, and potential for early detection. While challenges remain, ongoing research efforts are paving the way for their successful integration into clinical practice, ultimately benefiting patients through improved prognosis and personalized management strategies. This session will summarize the latest advancements in blood-based biomarkers for the diagnosis of HCC in the setting of chronic viral hepatitis, focusing on their diagnostic accuracy, clinical utility, and potential impact on patient care.

TERT Alterations in Virus-Induced Hepatocarcinogenesis: An Actionable Target?

Ju Hyun Shim

Univ. of Ulsan, Korea

Telomeres, the DNA-protein structures present at chromosome ends, are critical for genomic stability. As cells proliferate, telomeres shorten, eventually leading to cellular senescence or apoptosis. Telomerase, with its catalytic subunit encoded by the *TERT* gene, counteracts this shortening, maintaining telomere length and enabling cellular survival and proliferation. This becomes particularly relevant in the context of liver diseases, where the chronically damaged liver tissue undergoes repeated cycles of death and regeneration, potentiating telomere attrition.

In terms of telomere dynamics in hepatocarcinogenesis, chronic liver injury –whether due to viruses, alcohol, or metabolic factors– initiates a cascade of hepatic inflammation, oxidative stress, and cell death. These adverse conditions require the liver to regenerate continuously. Over time, this relentless compensatory cell renewal leads to progressive telomere shortening and replication senescence. This scenario paves the way for *TERT* genetic alterations, which can reactivate telomerase, thus maintaining telomere length and promoting cell survival. In the carcinogenic landscape, this signifies a transition towards malignancy.

Genetic mechanisms behind *TERT* reactivation in hepatocellular carcinoma (HCC) are as follows: 1) *TERT* promoter mutations; 2) viral integration; 3) *TERT* gene amplification; and 4) chromosomal rearrangement. *TERT* promoter mutations, located within the regulatory region upstream of the *TERT* gene, are among the most frequent genetic changes in HCC. They increase the gene's transcriptional activity, leading to reactivated telomerase and extended telomere lengths. Viral DNA, particularly of hepatitis B virus (HBV) and adeno-associated virus 2 (AAV2), integrates into the *TERT* promoter. This integration alters the promoter's regulatory landscape, enhancing *TERT* expression. It is estimated that around 30% of HCCs might harbor such viral insertions.

This presentation emphasizes the pivotal role of *TERT* promoter mutations and viral insertions into the *TERT* gene in primary liver cancers including HCC. Their prevalence and established connection to liver carcinogenesis make them potential therapeutic targets. By understanding these mechanisms, we could potentially devise interventions to counteract the carcinogenic pathway, providing new avenues for prevention and treatment of liver cancers, especially induced by viruses.

Molecular Signature and Immune Landscape of among HBV, HCV, and Non-Viral HCCs

Young-Sun Lee

Korea Univ. Korea

Hepatocellular Carcinoma (HCC) has been known for distinct molecular signatures and immune landscapes among HCCs associated with different etiologies, particularly Hepatitis B virus (HBV), Hepatitis C virus (HCV), and non-viral cause.[1]

Certain genetic mutation profiles and altered gene expression patterns are observed in individuals diagnosed with HBV-HCC. Molecular signatures causing HCC from chronic infections of HBV and HCV have been examined, providing insights into the pathways involved in hepatocellular carcinoma development.[2] MicroRNA expression between hepatitis B and hepatitis C showed significant difference, which lead disease progression to HCC.[3] Multidimensional analyses have identified distinct immune subsets enriched in both HBV-related and non-viral-related HCCs, emphasizing the importance of understanding the tumor microenvironment for potential therapeutic interventions.[4] Different immune responses to HBV, HCV, and non-viral HCC have implications for immunotherapy approaches. Understanding these differences can aid in the development of targeted treatments for each subtype of HCC.[5]

The molecular signatures and immune landscapes of HBV, HCV, and non-viral HCCs are distinct, offering valuable insights for personalized treatment strategies and advancing our understanding of hepatocellular carcinoma.

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Differential T-Cell Function between Viral and Non-Viral HCC during Immuno-Oncologic Therapy

Ji Won Han

The Catholic Univ. of Korea, Korea

The tendency of better clinical outcome in patients with viral etiologies have been reported in association with nivolumab[1], cabozantinib plus atezolizumab[2], and tremelimumab plus durvalumab[3] regimens. Of note, in updated efficacy and safety data from IMbrave150, Atezolizumab-bevacizumab (AB) treatment in patients with viral etiologies including hepatitis B virus (HBV) and hepatitis C virus (HCV) had superior overall survival (OS) and progression-free survival (PFS) compared to those treated with sorafenib, although subgroup analysis that only included AB treatment was not presented.[4] A recent meta-analysis which included 3 large randomized phase III trials of nivolumab, AB, and pembrolizumab, suggested that the immune-checkpoint inhibitor (ICI) regimen might be superior to the sorafenib in terms of OS in the HBV- and HCV-related hepatocellular carcinoma (HCC).[5] In addition, a recent network meta-analysis showed that patients with viral etiology showed significant survival benefit of the AB regimen compared to the tyrosine kinase inhibitors (TKIs).[6] A small-sized (n=66) recent real-world study showed that patients with viral etiologies have better OS and PFS than patients with non-viral etiology.[7] Another small-sized retrospective study (n=23) also showed that patients with viral etiology have higher ORR than those with non-viral etiology receiving AB treatment.[8] However, other real-world studies did not find differences between the two groups, therefore larger nationwide studies are needed to validate the previous data. In addition, whether there might be a difference between HBV and HCV in the clinical outcome of AB treatment and its related mechanism also needs to be clarified.

A recent experimental study showed that pathologic CD8+PD-1+ T cells might be associated with the limited role of anti-PD-1 treatment in NASH-related HCC [5]. Another study showed that hepatitis B virus (HBV)-infected subjects have distinct upregulation of peripheral blood inflammatory cytokine profiles, compared to the other etiologies including hepatitis C virus (HCV), NASH, and alcoholic liver diseases, suggesting different peripheral, intrahepatic, and intratumoral immune environments across the etiologies of HCC.[9] Elucidating the characteristics of CD8+ and CD4+ T cells, which are located in peripheral blood, tumors and surrounding tissues, is also important, because they are major effectors that respond to ICIs and kill tumor cells. However, it is unclear whether they respond to the ICIs differently according to the etiology, and whether these differential responses are associated with the clinical outcome. In this presentation, I would discuss about clues regarding this topic, using literature review and our own lab data.

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Policy Session (*K)

Chairs:

Young-Suk Lim (Univ. of Ulsan, Korea)
Jae Young Jang (Soonchunhyang Univ., Korea)

Introduction of the 1st National Strategic Plan for Viral Hepatitis B and C Control (2023-2027)

Jin Seon Yang

Korea Disease Control and Prevention Agency, Korea

1. Background

1) Disease Burden of Viral Hepatitis B and C

- Liver cancer ranks second in cancer deaths in Korea.
- Chronic viral hepatitis is responsible for approximately 70%* of liver cancer.

* 60% (Hepatitis B), 10% (Hepatitis C)

2) Implementation of a Global Goal to Eliminate Hepatitis

- (UN SDGs) By 2030, combat hepatitis, water-borne diseases and other communicable diseases
- (WHO) By 2030, aim to reduce new infections by 90% and deaths by 65%, as compared to 2015 levels

2. Korea's Hepatitis B Control

1) Introduced The National Immunization Program for hepatitis B in all infants (1995)

2) Implemented the Perinatal HBV Prevention Program (2002)

- The government covers the entire cost of immunoglobulin therapy, vaccination and HBsAg and anti-HBs tests for infants born to infected mothers.

3) WPRO certified that Korea achieved the regional Hepatitis B Control goal (2008)

- Korea became the first country in the Western Pacific Region to be certified by WHO for reaching the goal.

  → Overall Prevalence Rate: 7.2% in the 1980s → 2.7% in 2021

  → Prevalence rate among those aged 10-18: 4% in the 1980s → 0.0% in 2021

3. The 1st National Strategic Plan for Hepatitis B and C Control (2023-2027)

1) Vison : Build a healthy society, free from hepatitis

2) Goals : Reduce hepatitis deaths by 40% by 2027

- Hepatitis B deaths (per 100,000 population): 20.8 in 2015 → 12.5 in 2027
- Hepatitis C deaths (per 100,000 population): 2.5 in 2015 → 1.5 in 2027

3) Direction

- Create a proactive hepatitis control system encompassing the whole cycle*

* Prevention – Diagnosis – Treatment

4) 4 Strategics 12 Tasks

[1] Strengthening Proactive Hepatitis Prevention

1.1. Improve the management of perinatal hepatitis B infections by strengthening support for mothers not participating in the perinatal infection prevention program

1.2. Develop and implement customized awareness strategies for each target group

1.3. Enhance safety by tailoring guidelines for medication preparation spaces in healthcare facilities and reinforce the national blood management system, including investigating transfusion adverse reactions

[2] Active Detection and Management of Hepatitis

Patients

2.1. Promote the inclusion of hepatitis C in the National Health Screening Program for early detection

2.2. Establish a community-based system within local governments to detect and manage patients with hepatitis

2.3. Strengthen the management of untreated hepatitis C patients using a surveillance system

[3] Establishing Systematic Linkage to Care

3.1. Create a follow-up management system for the National and Private Health Screening

3.2. Build a system for the early detection of hepatitis in high-risk groups (such as North Korean defectors, inmates of correctional facilities, PWID, etc.) and linkages to care

[4] Strengthening the Foundation for Comprehensive Hepatitis Management

4.1. Establish governance to actively pursue the goal of eliminating hepatitis

4.2. Enhance collaboration between relevant Ministries to effectively address challenges

4.3. Foster cooperation with international organizations and groups supporting the global goal of hepatitis elimination.

4.4. Increase R&D investments, including developing therapeutics for hepatitis B and conducting cohort studies on hepatitis B and C patients

Hepatitis B and C Elimination Strategy in Korea

Chang Hun Lee

Jeonbuk National Univ., Korea

Introduction

The World Health Organization (WHO) recognizes viral hepatitis as a global public health problem and proposed the elimination of viral hepatitis as a goal to be achieved by 2030. In June 2021, WHO published an interim guideline that sets impact and programmatic targets for country validation of viral hepatitis elimination. WHO presented the criteria for elimination of viral hepatitis B and C for each country and prepared the corresponding guidelines. We calculated a domestic index associated with viral hepatitis elimination certifications. Based on this investigation, we aimed to set domestic goals for the elimination of viral hepatitis B and C and develop a domestic strategy that is in line with the WHO elimination strategy.

Hepatitis B elimination strategy

Hepatitis B appears to have reached the goal of elimination certification as the prevalence of hepatitis B surface antigen (HBsAg) under the age of 5 years in Korea. However, the prevalence of HBsAg is still high which is approximately 3%-5% among adults aged over 30 years. Moreover, the hepatitis B linkage to care rate is only about 39.4% and the treatment coverage is as low as 67.3%. Regarding liver-specific mortality, the annual mortality rate is as high as 18.85 per 100,000 people, and liver cancer accounts for 54% of the deaths. We propose strategies to increase the linkage to care rate by strengthening the post-screening management of the current Hepatitis B screening program. Moreover, it underscores the importance of elevating treatment rates, expanding the scope of treatment targets, and ultimately preventing the progression of liver diseases and the onset of liver cancer. The overarching goal is to reduce mortality rates by preventing the occurrence of liver-related complications through improved diagnosis, treatment, and comprehensive care management.

Hepatitis C elimination strategy

The annual incidence of hepatitis C remains high at 11.9 per 100,000 people in Korea, whereas the hepatitis C linkage to care rate and the treatment rate are low (65.5% and 56.8%, respectively). Regarding the liver-specific mortality rate, the annual mortality rate for hepatitis C is 2.02 per 100,000 people. To achieve the eradication of hepatitis C, it is crucial to prioritize a strategy that involves the introduction of Hepatitis C screening in national health examinations. This step aims to diagnose asymptomatic Hepatitis C patients and establish a system that connects them to antiviral treatment. Additionally, this strategy aims to reduce the incidence of hepatitis C and lower the liver-related mortality by enhancing hepatitis C treatment coverage through treatment linkage. Furthermore, it is proposed to establish a hepatitis C management plan for persons who inject drugs (PWID).

Conclusions

In order to accomplish the elimination of viral hepatitis, it is crucial to proficiently carry out the domestic strategy for viral hepatitis elimination. This involves

setting up a comprehensive management system that involves collaboration between the government and relevant experts. Additionally, consistent and sustained government support is crucial for the successful execution of the domestic viral hepatitis elimination strategy.

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Korean HCV Cohort Study and People Who Inject Drugs (PWID) in Korea

Gwang Hyeon Choi

Seoul National Univ., Korea

The Korea hepatitis C virus (HCV) cohort study commenced in 2007 with the participation of four hospitals, including Seoul National University Bundang Hospital. Currently, the study has expanded to include 10 hospitals. A distinctive feature of this cohort study is that the National Cancer Center is responsible for data purification and quality control. The primary objective of this study is to survey infection risk factors and concurrent diseases among adults aged 19 years or older who are anti-HCV positive. It involves collecting blood samples, monitoring treatment progress, and tracking occurrences of liver cancer and mortality. The HCV cohort study has yielded valuable insights into the epidemiological and clinical characteristics of HCV infection in South Korea, as well as the topics of HCC, decompensation, mortality reduction following direct acting antiviral (DAA) treatment, and the epidemiology and treatment status of Person who inject drug (PWID), which have been published in papers and presented at numerous academic forums.

In contrast, the Korea PWID-HCV study was initiated in 2022 at three hospitals, with Seoul National University Bundang Hospital serving as the principal research institution. This study focuses on conducting anti-HCV screening tests and administering questionnaires to PWID patients. The aim is to raise awareness among PWID-HCV patients about their treatment requirements and to monitor their treatment progress. This approach is expected to shed light on the HCV cascade of care among PWID patients, helping to identify HCV prevalence and treatment statuses. We anticipate sharing HCV prevalence results based on retrospective and prospective data in the near future.

In conclusion, the two studies are expected to serve as a good basis for deriving the core indices for HCV elimination presented by WHO.

Korean HBV Cohort Study

Jun Yong Park

Yonsei Univ., Korea

Background and Aim: We aimed to report the clinical outcome of Korean chronic hepatitis B (CHB) patients from a prospective longitudinal cohort.

Methods: This cohort, supported by the Korea Disease Control and Prevention Agency (2022E190400), was established in 2015. Voluntarily enrolled patients with CHB serially provide their clinical data and blood samples during the ten-year follow-up.

Results: From 2015 to 2022, 2949 patients (1812 male) with a mean age of 52.6 years participated in this study. Annual 16 mL of blood sampling was collected (median three times) from 1391 volunteers. Male patients had more smoking and hazardous alcohol intake (P<0.001). At the enrollment, most patients were receiving antiviral therapy (AVT) (n=2359, 80.0%), whereas 515 (17.4%) patients were AVT-naïve. Cirrhosis was noted in 646 (21.9%) patients. The most favored AVT regimen was tenofovir disoproxyl fumarate (TDF) (40.0%), followed by entecavir (33.0%). However, during the recent two years, an increasing proportion of patients are starting the first AVT with tenofovir alafenamide (5.9% to 13.5%) or besifovir dipivoxil maleate (2.8% to 7.5%). Most patients receiving AVT with a high-genetic barrier experienced a complete virologic response (more than 80% at week 48). Crudely, the incidence of an increase in chronic kidney disease stage ≥1 was significantly higher in TDF users than ETV users (7.56 vs. 4.56 per 100 person-years, P<0.001). Hepatocellular carcinoma occurred in 33 (1.9%) patients after 50.3 months of median follow-up, most of which were within Milan criteria. Cirrhosis was independently associated with hepatocellular carcinoma occur (adjusted hazard ratio, 5.005, P=0.002).

Conclusion: This cohort study will evaluate long-term liver-related outcomes among Korean CHB patients. Future research using the cohort data and blood samples after the data purification could reveal the unmet needs to manage CHB.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Symposium 2-1. Circulating HBV Markers: What Are Their Roles?

Chairs:

Tarik Asselah (Hepatology at Hôpital Beaujon, France)
Jung-Hwan Yoon (Seoul National Univ., Korea)

Ultra-High Sensitivity HBsAg and Anti-HBc in Managing Chronic Hepatitis B

Jihyun An

Hanyang Univ., Korea

Hepatitis B virus (HBV) infection can lead to severe liver complications such as chronic hepatitis B (CHB), cirrhosis, and liver cancer, highlighting a pressing global health issue. As the therapeutic landscape evolves with several novel treatments targeting HBV or its immune responses in the pipeline, the identification and utility of HBV biomarkers have become paramount. These biomarkers are crucial in understanding the infection's course, predicting disease progression, and gauging the efficacy of both existing and emerging treatments. Therefore, advancing our knowledge of these markers can pave the way for improved therapeutic outcomes in CHB patients.

Ideal biomarkers play an indispensable role in guiding clinical decisions, offering insights that are early, accurate, and indicative of a potential clinical trajectory. For a biomarker to be considered optimal, it should not only be predictive but also specific, sensitive, unaffected by HBV genotypes, and reflective of the disease's activity and severity. Moreover, it should be easily measurable, cost-effective, quick to procure, and non-invasive.

In the context of HBV infections, several serum markers, such as HBV DNA, HBV core-related antigen, and HBV RNA, have emerged as potential indicators of intrahepatic viral activity. Recently, the utility of HBsAg assays, especially the ultra-high sensitive HBsAg assay, alongside ant-HBc, is gaining clinical prominence. Their potential in delineating the course of HBV infection, forecasting disease progression, estimating the risk of HBV reactivation post-treatment cessation or during immunosuppression, and evaluating the efficacy of both current and novel therapeutic regimes is garnering interest.

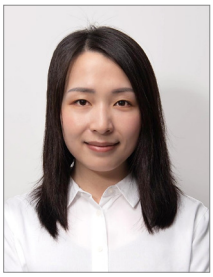
HBsAg assays including ultra-high sensitivity HBsAg assays

Hepatitis B surface antigen (HBsAg) is a secreted envelope protein continuously released into the bloodstream during HBV infection, irrespective of viral replication. Recent advances in HBsAg quantification have illustrated a correlation between HBsAg levels and intrahepatic covalently closed circular DNA (cccDNA), which serves as a template for viral transcription and underlies chronic HBV infection. Notably, a link between HBsAg levels and HBV DNA suggests that HBsAg quantification might function as a surrogate marker for the immune control of viral replication.

Recently, a semi-automated, ultra-high sensitivity immune complex transfer chemiluminescence enzyme immunoassay for HBsAg has been introduced. With a cut-off value of 0.0005 IU/ml, this assay boasts a specificity ranging between 99.5% and 100%. For patients who have resolved HBV infection and are undergoing systemic chemotherapy or immunosuppressive therapies, particularly with anti-CD20 antibodies, the ultra-high sensitivity HBsAg assay emerges as a potent diagnostic tool. It holds promise not merely for baseline screening but also as a means to monitor and preempt HBV reactivation-related hepatitis.

Anti-HBc

Detection of anti-HBc in serum is widely accepted as a surrogate biomarker for occult HBV infection, particularly in blood and organ donors, as well as in individuals commencing immunosuppressive regimens.There is a discernible correlation between serum anti-HBc levels and the presence of cccDNA. Elevated baseline concentrations of anti-HBc have been identified as potential predictors of HBV reactivation in lymphoma patients with previously resolved HBV infections who are undergoing B-cell-depleting chemotherapy. Although the quantification of anti-HBc and the analysis of circulating HBV-specific T cells present promising avenues in HBsAg-negative patients, their definitive utility as biomarkers warrants additional validation, especially within the context of occult HBV infection.



HBcrAg and HBV RNA in Managing Chronic Hepatitis B

Lung-Yi Mak

The Univ. of Hong Kong, Hong Kong

Chronic hepatitis B infection is a major public health challenge. With the advancement in technology, various components of the viral cycle can now be measured in the blood to assess viral activity. Viral nucleic acids in the form of encapsidated pre-genomic RNA (pgRNA), can be measured in the serum. Hepatitis B core-related antigen (HBcrAg) is a viral translational product that consists of 3 related proteins (hepatitis B core antigen, hepatitis B e antigen, and a truncated 22 kDa precure protein). The profile of pgRNA and HBcrAg in different phases of the natural history as well as under antiviral therapy has been characterized. The primary role of these markers include risk prediction for hepatocellular carcinoma (HCC) and risk stratification for partial cure, defined as off-therapy virological control, or functional cure, defined as hepatitis B surface antigen (HBsAg) seroclearance plus unquantifiable serum HBV DNA for ≥6 months. They are important in predicting clinical outcomes including HCC risk and partial/ functional cure. As the primary outcome of phase III trials in CHB is set as HBsAg seroclearance, novel viral biomarkers can help assess target engagement and potentially inform the efficacy of novel compounds. Early viral biomarker response can help with prioritization of subjects into clinical trials. However, standardization and validation studies would be crucial before viral biomarkers can be broadly implemented in clinical use.

Circulating Virus-Host Chimera DNA for Monitoring Virus-Related HCC

Shiou-Hwei Yeh

National Taiwan Univ., Taiwan

Curative treatment of HCC depends on early diagnosis of HCC, which is very limited for HCC patients. Instead, identifying cases that respond to targeted or immunotherapies is an urgent unmet need for advanced HCC. We propose that HBV integration in HCC might shed light on these two important issues. HBV DNA integration is present in approximately 90% of HBV-HCC and occurs at random locations on human chromosomes, which is therefore a signature DNA marker for individual HCC. Detection of virus-host chimera DNA (vh-chimera DNA) generated from junctions of HBV integration on HCC chromosome in plasma could be a cell-free tumor-specific DNA (ctDNA) biomarker for each HCC. We have validated this hypothesis, showing the level of HCC vh-DNA (by capture-NGS) found in plasma samples (by ddPCR) well correlated with tumor sizes, with a detection limit of 1.5 cm. This platform was already successfully applied for early detection of recurrent HCC after curative tumor therapy. As noted, integration in HCC occurs at hotspots close to the TERT and MLL4 genes, suggesting a strong positive selection of HBV-integrated hepatocytes at both oncogenes to progress to HCC. Interestingly, three mutually exclusive mutations were identified in HBV-HCC, i.e., integration of HBV DNA into the TERT promoter, integration of HBV DNA into MLL4, or TERT promoter point mutations, which can be used to classify HBV-HCC into four groups. Transcriptomic analyses showed that these four HCC subgroups had distinct expression profiles, suggesting different oncogenic pathways. An active immune signature associated with immune checkpoint inhibitor treatment response was identified in one subgroup, which has the potential to guide immunotherapy and warrants validation in HCC patients. In summary, HBV integration not only provides a new ctDNA biomarker for monitoring HCC, but also helps guide effective therapy. Meanwhile, our new classification provides a simple and robust genetic classification that helps to understand the new biology of HBV-HCC and to harmonize clinical studies.

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APASL STC 2023 BUSAN

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"Toward Elimination of Viral Hepatitis"

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DAY 2 | Friday, Sept. 22, 2023

Symposium 2-4. Direction to Pursue in Hepatitis C Treatment

Chairs:

Chun-Jen Liu (National Taiwan Univ., Taiwan)
Seung Woon Paik (Sungkyunkwan Univ., Korea)

How to Manage Patients with DAA Treatment Failure

Young-Joo Jin
Inha Univ., Korea

Failure to respond to the current highly potent DAA-based regimens for HCV infection is today an uncommon occurrence. However, assuming a less than 2% failure rate, the number of patients who will need re-treatment becomes considerable given the large number of patients receiving antiviral therapy. In addition, considering the clinical significance of SVR achievement even in HCV patients with prior DAA treatment failure, it is necessary to know how to manage these patients.

Currently, available drugs are Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) or Glecaprevir/Pibretasvir (G/P). Based on POLARIS-1 and -4 trials, the SOF/VEL/VOX 12-week regimen is effective for patients with DAA experience, including treatment with NS5A and non-NS5A inhibitors. SOF/VEL/VOX 12-week treatment showed a high SVR achievement rate and excellent tolerability, even for G1 HCV pts. (including patients with compensated cirrhosis) who had NS5A/NS5B inhibitor treatment experience and failed previous treatment. However, SOF/VEL/VOX is not recommended in decompensated LC patients. In the MAGELLAN trials, HCV patients with treatment failure to at least one DAA-containing treatment were analyzed. In the MAGELAN I trial, G/P is not recommended for the re-treatment of patients with prior exposure to both NS3/4A- and NS5A inhibitors. In the MAGELLAN-3 trial, patients who previously failed G/P due to virologic failure were retreated with G/P + SOF + RBV and achieved SVR12 of 97%.

In the AASLD-IDSA guideline, for patients with SOF-based treatment failures, SOV/VEL/VOX for 12 weeks is recommended. For patients with G/P treatment failures, G/P plus SOF and RBV for 16 16-week regimens or SOV/VEL/VOX for 12wks regimens is recommended. For patients with SOF/VEL/VOX treatmemt failures, G/P plus SOF and RBV for a 16-week regimen or SOV/VEL/VOX plus RBV for a 24-week regimen is recommended.

In the EASL guideline, Patients who have no predictors of low response should be retreated with the fixed-dose combination of SOF/VEL/VOX for 12 weeks (A1). Patients who have predictors of lower response (advanced liver disease, multiple courses of DAA-based treatment, complex NS5A RAS profile) can be retreated with the combination G/P plus SOF for 12 weeks, based on an individual multidisciplinary decision (B1). In very difficult-to-cure patients (patients with NS5A RASs who failed twice or more to achieve SVR after a combination regimen including a protease and/or an NS5A inhibitor), the triple combination of SOF/VEL/VOX or the triple combination of SOF+G/P can be administered for 12 weeks with weight-based RBV, and/or treatment duration can be prolonged to 16 to 24 weeks, based on an individual multidisciplinary decision (B1). In patients who failed to achieve SVR after retreatment with the triple combination of SOF/VEL/VOX, the triple combination of SOF+G/P can be administered for 24 weeks with weight-based RBV (B1).

Several factors, such as a previous treatment history of NS3 PI, NS5A inhibitor, a combination of both, NS5B polymerase inhibitor, or RAS for PI or NS5A inhibitor, GT, or liver cirrhosis should be considered for re-treatment for HCV patients with prior DAA treatment failure. Considering these factors, G/P, SOF/VEL/VOX with or without SOF or RBV combination can be selectively used for HCV patients with prior DAA treatment failure.

How to Manage Difficult-to-Cure Patients: Decompensated Disease and Transplantation

In Hee Kim

Jeonbuk National Univ., Korea

The advent of direct-acting antivirals (DAA) revolutionized the therapy for hepatitis C virus (HCV) infection showing high rates of sustained virologic response (SVR) with good safety. It has improved the treatment outcomes of hepatitis C in patients with decompensated cirrhosis and post-transplantation, which have been difficult to treat.

DAAs treatment in patients with decompensated cirrhosis

The fixed-dose combination of sofosbuvir (SOF)/velpatasvir (VEL) is the treatment of choice for patients with decompensated cirrhosis.[1-3] For patients with genotype 1-6 and ribavirin (RBV) eligible, the fixed-dose combination of SOF/VEL with weight-based RBV for 12 weeks is recommended. Patients who are RBV ineligible should receive the fixed-dose combination of SOF/VEL for 24 weeks without RBV. Patients with decompensated cirrhosis in whom prior SOF- or NS-5A inhibitor-based treatment failed can be treated the fixed-dose combination of SOF/VEL with weight-based RBV for 24 weeks (for genotype 1-6). Clinical trials demonstrated that patients with decompensated cirrhosis receiving DAA therapy achieve high SVR and experience improvement in liver function between baseline and posttreatment week 12.[4-6] However, improvements may be insufficient to avoid liver-related death or the need for liver transplantation (LT).[7,8] Predictors of improvement or decline have not been clearly identified, although patients with a baseline MELD score >18-20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than antiviral treatment.[3,7-10] According to the recommendations of the EASL guideline, patients with decompensated cirrhosis without HCC awaiting LT with a MELD score <18-20 should be treated prior to LT.[3] Whereas, patients with decompensated cirrhosis without HCC awaiting LT with a MELD score >18-20 should be transplanted first, without antiviral treatment, and HCV infection should be treated after LT. Recently, several studies investigated the long-term clinical outcome following DAA therapy in HCV-related advanced cirrhosis. These data highlight that a proportion of patients with advanced cirrhosis who receive DAA therapy may not achieve significant long-term improvement in liver function. Overall, listing rates for HCV patients have decreased in the DAA era. However, delisting due to clinical improvement remains low and significant morbidity may persist in some patients over the long term, despite SVR.[11]

DAA treatment in recipients with transplantation

All patients with post-transplant recurrence of HCV infection must be treated. Treatment should be initiated early after liver transplantation, ideally as early as possible when the patient s stabilized, because the SVR12 rates diminish in patients with advanced post-transplant liver disease. Patients with post liver and kidney transplant HCV recurrence (genotype 1-6) without cirrhosis or with compensated cirrhosis should be treat-

ed with either the fixed-dose combination of SOF/VEL for 12 weeks or the fixed-dose combination of glecaprevir (GLE)/pibrentasvir (PIB) for 12 weeks.[1-3] Patients with post-transplant HCV recurrence with decompensated cirrhosis should be treated with the fixed-dose combination of SOF/VEL with weight-based RBV for 12 weeks. Patients with decompensated cirrhosis and with contraindications for RBV, or with poor tolerance to RBV on treatment, should be treated with the fixed dose combination of SOF/VEL for 24 weeks without RBV. Important drug–drug interactions unique to the posttransplant setting should be addressed prior to initiation of DAA therapy. Coadministration of GLE/PIB and cyclosporine >100 mg/d is not recommended.

Based on studies supporting the safety and efficacy of DAA treatment after transplantation, many transplant centers have begun using organs from HCV-positive donors in HCV-negative transplant recipients to address the issue of imbalance between transplant recipients and deceased donors.[12,13] The use of HCV-positive organs has been shown to be an effective strategy for increasing access to transplantation and reducing wait-list time and overall mortality. Emerging data support HCV treatment as early as possible when transplanting an HCV-viremic liver graft into an HCV-seronegative recipient.[14] HCV treatment also should begin as soon as possible in HCV-seronegative patients who undergo transplantation with a non-liver graft from an HCV-viremic donor. This strategy reduces the likelihood of hepatic and extrahepatic HCV-related complications in the immediate posttransplant period. Data evaluating longer-term patient outcomes after transplantation with an HCV-viremic donor organ have shown encouraging results. In an analysis of the United Network for Organ Sharing database, HCV-negative liver transplant patients who received the graft from an HCV-positive donor (viremic and nonviremic) were shown to have superior 1-year graft survival rates compared with those who received a graft from an HCV-negative donor.[15] Extensive informed consent, and shared decision-making between the patient and clinical team should occur prior to transplantation of an HCV-viremic organ into an HCV-negative recipient.

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Managing Drug-Drug Interaction, Adherence, and Adverse Events in the Era of Pangenotypic DAA

Woo Jin Chung

Keimyung Univ., Korea

Several studies confirmed that direct acting antivirals (DAAs) are highly effective in treating chronic hepatitis C virus (HCV) infected patients. These studies possessed several unique characteristics including drug-drug interactions, adherence and adverse events compared with peg-interferon containing regimens.

Each DAA has its own metabolism and drug-drug interactions (DDIs), and managing them is a hallenge. The key to interpret DDI data is a good understanding of the pharmacokinetic profiles of the drug involved. Their ability to inhibit CYTP450-3A4 and transporters can have significant clinical sequences.1

Adherence to treatment is important, and managing any condition or circumstance that may affect adherence to treatment is recommended before commencing DAA therapy. Strong adherence and sustained virological responses (SVR) with DAA is achievable, with appropriate supports, even in the context of substance use, and complex health/social issues.

DAA exposure may not be associated with higher rates of any serious adverse events, including those relateds to liver, kidney, and cardiovascular systems, and was associated with lower odds of experiencing the adverse events.

Chronic HCV infection can be cure with antiviral therapy. Chronic HCV infected patients who were cured have a lower rate of complications. In contrast, in the rate of complications was not related to virological cure among those with cirrhotic patients even with decompensated state.

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Multidisciplinary Approach to Predict Fibrosis Progression and HCC after DAA Therapy

Tawesak Tanwandee

Mahidol Univ., Thailand

Chronic hepatitis V (HCV) is among the most important cause of liver cirrhosis and hepatocellular carcinoma (HCC) as well as leading indication of liver transplantation worldwide. Treatment of HCV with the result of sustained virological response (SVR) has been proven to improve outcomes of all stages of HCV related liver disease, especially in compensated stage. The availability of direct acting anti-viral (DAA) has accelerated HCV treatment, however, maximum benefit of HCV treatment probably can be obtained before the patients become cirrhotic, namely compensated advanced chronic liver disease (cACLD).

There are several approaches to predict fibrosis progression and HCC in chronic hepatitis C patients who have achieved SVR. These parameters can be obtained before treatment initiation or after treatment with SVR. These parameters include.

1. Liver fibrosis/cirrhosis status, usually assessed by elastography, non-invasive liver fibrosis indexes both direct and indirect biomarkers such as FIB-4, the more fibrosis index, the higher the HCC development.
2. Portal hypertension which usually also assessed by non-invasive tools like elastography and platelet count.
3. Liver synthetic function like albumin
4. Risk prediction models which include many of the above parameters to separate low risk of developing HCC from high-risk patients, this propose mainly looks at cost-effective of HCC screening in these patients after achieving SVR. Some of these models are shown in table 1.
5. Molecular signature to predict long-term fibrosis progression where these transcriptome-based parameters share with other causes of liver fibrosis.
6. Continued exposure to other causes of liver fibrosis including metabolic associated fatty liver disease and unhealthy consumption of alcohol.
7. Treatment with statin associated with less progressive disease.

Conclusion: HCV who achieve SVR after treatment has overall impact on the patient outcomes, however, the patients who have baseline advance liver disease may progress, especially those who continue to expose with other causes of liver injury. Moreover, HCC risk remains even after SVR and there are several non-invasive models using multimodality approach and parameters developed to stratify risk and make HCC screening more cost effective.

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Table 1. Validate models for HCC risk prediction after SVR in patients with HCV

Study	Score Name	Variable	HCC predictors	Risk class	Cumulative incidence (%)
Fan et al. 2020	aMAP	Age, sex, albumin, bilirubin, PLT	ALBI score	<50 low 50-60 Medium >60 high	3 or 5 years low 0-0.8%, medium 1.5-4.8, high 8.1-19.9
Shiha et al. 2020	GES	Age, sex, albumin, AFP, pretreatment fibrosis (F3, 4)	Male >54 Albumin <3.8 g/dL, AFP >20 ng/dL, F4	GES <6 low 6-7.5 intermediate >7.5 high	1,2,3 year Low 0.1/1.2/1.9 Intermediate 0.7/3.3/5.8 High 1.2/7.1/9.5
Hiraoka et al. 2019	ADRES	Sex, SVR24 FIB-4, SVR 24 AFP	Male, FIB-4>3.25, AFP >5 ng/dL	ADRES0/1/2/3	ADRES 0/1/2/3 0/0.5/8.4/18 at 1 year
Ioannou et al. 2018	VHA	Sex, age, BMI, ethnicity, HCV genotype, Hb, PLT, albumin, INR, AST/√ALT	Age >60 PLT<61x10^4 AST/√ALT>8.8 in non-cirrhotic, >11.01 in cirrhotic Albumin <2.9 g/dL	4 subgroups -Cirrhosis/SVR -Cirrhosis/no SVR -No cirrhosis/SVR -No cirrhosis/no SVR	 -4.5% at 2 years -13.1% at 2.6 year -0.7% at 2.3 year -4.2% at 3.7 year
Semmler G et al. 2022	AFP/LSM/ Albumin-based	AFP, age, LSM, albumin, optional alcohol	AFP>4.6: 3 Age ≥59:2 LSM ≥19:1 Albumin <42 g/L:1 Optional alcohol >30/20 gm/d:2	High-risk ≥4	Low 3.3 High 17.5
Semmler G et al. 2022	LSM/ albumin-based	Age, LSM, albumin, optional alcohol	Age ≥59:3 LSM ≥19:2 Albumin <42 g/L:2 Optional alcohol >30/20 gm/d:2	High-risk ≥4	Low 3.7 High 11.6

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

State-of-the-Art Lecture 2

Chair:
Jin Mo Yang (The Catholic Univ. of Korea, Korea)

The Road to Curing Hepatitis B Virus Infection: Past, Present, and Future

George Lau

Humanity and Health Medical Group, Hong Kong

As a practicing hepatologist in Asia Pacific, the major clinical challenge remains the combat against acute-on-chronic liver failure (ACLF), end-staged liver cirrhosis (ESLC) and hepatocellular carcinoma (HCC), mainly due to underlying chronic viral hepatitis B (CHB). Seeking a "CURE" for these patients have always been a dream for all clinical researcher and physician engaged in the management of liver diseases. Up till 2016, eight therapies, namely interferon, pegylated interferon (pIFN) α2a, lamivudine, adefovir, telbivudine, entecavir, tenofovir and tenofovir alafenamide, has been registered as effective treatment for CHB, with its indication clearly delineated by authoritative liver societies (AASLD, APASL, EASL). The use of these therapies can effectively suppress viral replication, with a drastic risk reduction of ACLF, ESLC and HCC. As demonstrated by our group, loss of HBsAg -functional cure, the current recommended criteria to stop therapy, could only occur with restoration of host immunity against the virus. To this end, the current registered agents can provide only very limited success. Monotherapy with 48 weeks of pIFNα2a confers functional cure in 3% and 8% in HBeAg positive and HBeAg negative CHB patients, respectively. Prolonged high-resistant barrier nucleosid(t)e analogue (NUCs) results in <1%/year functional cure. As a result, the majority of CHB patients need to receive life-long NUCs therapy, which might reciprocally impede restoration of effective host immunity against HBV. In keeping with this, a recent large cohort study with 10-year follow-up demonstrated that finite NUC therapy in HBeAg-negative CHB reduce HCC incidence, increase HBsAg loss and improve survival. On the other hand, to enhance "functional cure" in NUCs-treated CHB, de novo, sequential and add-on pIFNα2a have been attempted. Notably, functional cure can be sustained in one-quarter of CHB patients with 96 weeks of pIFN pIFNα2a and low levels of hepatitis B core-related antigen and higher levels of hepatitis B surface antibodies at the end of treatment are linked to durable functional cure. In the past few years, new drugs are being explored but with limited success, due to the presence of covalently closed circular and integrated HBV DNA. This is further compounded by the recent revelation of additional "unknown confounding factors" which deter functional cure as reported by the phase 2 CLEAR-B studies. In essence, a highly selected group of CHB treated with NUCs randomly assigned to group 1,2 3 who received the same treatment (, n group 3 (16%) vs group 1 (34%, p=0.01) vs group 2 (37%, p=0.005), suggesting the presence of "unknown confounding factor" which deter functional cure. This need to be explained. Despite the availability of therapy which can effectively suppress HBV replication only 2·4% of CHB have been treated worldwide. This lack of treatment could largely explain the high and rising prevalence of HCC in 2020 with an estimated of 450,000 cases and 410,000 deaths from liver cancer in Eastern Asia. More emphasis should hence be placed on improving the public awareness with better

screening and identification of patients with CHB. In addition with the drastic reduction of cost of therapy, new data suggesting that those CHB previously not indicated for therapy could benefit from treatment, a broadening of the current indication for anti-HBV therapy should be considered in future CHB guidelines to enable us to achieve WHO's global hepatitis strategy, endorsed by all WHO Member States, to reduce new hepatitis infections by 90% and deaths by 65% between 2016 and 2030.

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DAY 2 | Friday, Sept. 22, 2023

Keynote Lecture 2. Cure of viral hepatitis. Is This Safe against the Development of HCC?

Chairs:

Jia-Horng Kao (National Taiwan Univ., Taiwan)
Kyung-Suk Suh (Seoul National Univ., Korea)

Genetic Polymorphism and Family History as a Non-Modifiable Risk Factor for HCC after HBV Cure

Yoon Jun Kim

Seoul National Univ., Korea

Hepatocellular Carcinoma (HCC) remains a significant global health concern, especially in regions with a high prevalence of Hepatitis B Virus (HBV) infection. While successful HBV treatment through antiviral therapy has shown promise in reducing HCC risk, certain individuals continue to face susceptibility to HCC development even after viral clearance. This lecture explores the role of genetic polymorphism and family history as non-modifiable risk factors in post-HBV cure HCC development. Genetic variations in key pathways implicated in carcinogenesis, combined with a familial predisposition, can contribute to an elevated risk of HCC. Understanding the intricate interplay between genetic factors and family history is essential for identifying high-risk populations and tailoring effective surveillance strategies to mitigate HCC recurrence following HBV cure. Further research into the molecular mechanisms underlying these risk factors could pave the way for personalized interventions and early detection strategies, ultimately improving outcomes for individuals vulnerable to HCC post-HBV cure. In this lecture, the current studies regarding Genetic polymorphism and family history as a non-modifiable risk factor for HCC after HBV cure will be discussed.

Viral Persistence after a Functional Cure and HCC Risk

Jia-Horng Kao

National Taiwan Univ., Taiwan

Hepatitis B virus (HBV) is responsible for more than 50% of hepatocellular carcinoma (HCC) in HBV hyperendemic areas, such as the Asia-Pacific region. In untreated and treated patients with chronic HBV infection, HBsAg seroclearance or "functional cure" has been reported to confer a very favorable clinical outcome with a significantly reduced HCC risk. However, recent studies showed that HCC risk still persists in chronic hepatitis B (CHB) patients after HBsAg seroclearance, whereas the risk of hepatic decompensation decreases over time. Further analysis showed that age and gender may affect HCC risk after HBsAg seroclearance. For example, female patients aged 50 years or below have zero risk of HCC after HBsAg seroclearance, whereas female patients aged above 50 years and all male patients are still at risk of HCC. Whether viral persistence after a functional cure increases HCC risk remains unclear and deserves further discussion. Two forms of viral persistence including occult HBV infection (OBI) and HBV DNA integration can exist after HBsAg seroclearance. It is widely debated whether OBI may accelerate the disease progression toward the development of HCC. Although OBI potentially maintains the pro-oncogenic properties of HBV, it is believed that the OBI-related HCC risk, if exists, is very limited. HBV DNA integration into chromosomes is an incidental event during HBV infection; however, it becomes the most common somatic mutation in the majority of HBV-related HCC cases. Approximately 90% of HBV-related HCC cells contain integrated HBV DNA, usually at multiple chromosomal sites. Whole genome sequencing of liver tissues from CHB patients showed integration occurring at random positions in human chromosomes; however, in the genomes of HBV-related HCC patients, there are integration hotspots. Both the enrichment of the HBV-integration proportion in HCC and the emergence of integration hotspots suggest a strong positive selection of HBV-integrated hepatocytes to progress to HCC. The activation of HBV integration hotspot genes, such as telomerase (TERT) or histone methyltransferase (MLL4/KMT2B), resembles insertional mutagenesis by oncogenic animal retroviruses. Novel HBV therapy should target integrated HBV DNA to reduce HCC risk in CHB patients with overt or occult HBV infection.

Mechanisms of Hepatocarcinogenesis after HCV Eradication

Raymond T. Chung

Harvard Univ., USA

Hepatocellular carcinoma (HCC), the most common hepatic malignancy, is the third leading cause of cancer death worldwide.[1] The primary risk factor for HCC is chronic viral hepatitis.[2] Infection with hepatitis C virus (HCV) affects 58 million people worldwide and represents a leading cause of chronic liver disease, HCC, liver transplantation, and liver-related mortality.[3] Highly effective and well-tolerated oral direct-acting antiviral (DAA) therapy for HCV has become widely available and, accordingly, the World Health Organization has set a goal of eliminating HCV as a major public health threat by 2030.[4] As more patients with HCV achieve cure, the management of established liver disease in those who experience sustained virologic response (SVR) becomes a growing challenge.[5] Despite HCV cure, the risk for HCC in patients with advanced fibrosis or cirrhosis is reduced but not eliminated and persists over the long term.[6-13] Multiple mechanisms for persistent HCC risk after SVR have been implicated, including direct and indirect viral effects. For patients with advanced fibrosis or cirrhosis, HCC surveillance strategies should continue as the population in whom surveillance can safely discontinue has not yet been established.[14] While HCC risk persists after HCV cure, opportunities for risk stratification and risk reduction strategies have emerged.

Persistent HCC risk after SVR. Infection with hepatitis B virus (HBV) and HCV are the major risk factors for the development of HCC. HBV is the most prominent risk factor for HCC, accounting for approximately 33% of liver cancer deaths globally.[3,15] As a DNA virus, HBV can induce HCC as a result of insertional mutagenesis in patients without advanced liver disease. Unlike HBV infection, HCV requires advanced fibrosis or cirrhosis for the development of HCC in nearly all cases and, for patients with cirrhosis, portends a 1-4% annual risk of HCC.[16,17] The benefits of HCV elimination are well-established for patients with and without cirrhosis, including reductions in liver decompensation, liver-related mortality, and all-cause mortality.[18-22] Similar benefits have been shown for patients cured of HCV with DAA therapy across multiple clinical and geographic scenarios.[23-27] In addition, HCV cure is associated with improved quality of life and reduced morbidity from extrahepatic manifestations of HCV including renal, dermatologic, and metabolic complications.[28]

While the risk of HCC is sharply reduced after HCV cure, it is not eliminated, particularly for those with established cirrhosis and is similar for patients treated with DAA and interferon-based therapy.[7-13] In a multivariable analysis of a large cohort of patients from the Veterans Affairs national healthcare system treated with DAA therapy, SVR was associated with a reduced hazard ratio (HR) for new HCC (0.29, 95% confidence interval [CI] 0.23-0.37).[9] In a similar Veterans Affairs cohort, patients with cirrhosis and pre-SVR fibrosis-4 (FIB-4) score ≥3.25 treated with DAA therapy had an annual incidence of HCC 3.66% per year compared to those with a pre-SVR FIB-4 score <3.25 of 1.16%

per year.[13] For patients with cirrhosis and FIB-4 score ≥3.25, the annual HCC risk decreased from 3.8% per year in the first year after SVR to 2.4% per year by the fourth year.[13] In this study, a decrease in FIB-4 score from ≥3.25 pre-SVR to <3.25 post-SVR was associated with approximately 50% lower risk of HCC however the absolute annual HCC risk remained above 2% per year. Importantly, HCC risk persisted for at least 10 years in patients achieving SVR. Meta-analysis have suggested that the incidence of HCC may decrease over time after HCC cure and be lower for patients with a lesser extent of fibrosis, younger age, and absence of prior decompensation.[29]

Mechanisms of post-SVR hepatocarcinogenesis. While hepatocarcinogenesis in HBV infection is in part related to genetic alterations induced by viral integration into the host genome, HCV does not insert into the host genome; it thus contributes to hepatocarcinogenesis via alternate mechanisms (Figure 1).[30,31] Multiple mechanisms for post-SVR hepatocarcinogenesis have been proposed, including direct non-insertional genetic changes, virus-induced proliferative and anti-apoptotic signaling, contribution of hepatotoxic cofactors, and epigenetic changes (Table 1). Mutations in human HCC are frequent, genome-wide and support a stochastic model of genotoxic events. HCV infection induces changes in protein expression and immune response that together promote genotoxic reactive oxygen species. Such DNA-damaging oxidative stress is an important risk factor in the development of HCC and may persist post-SVR and interact with cofactors that themselves promote oxidative stress, including established steatosis, alcohol (and associated metabolites), iron, and other viral infections (particularly HBV) leading to genomic instability and further activation of growth pathways en route to HCC development.

Virus-induced proliferation and anti-apoptotic signaling have been shown through multiple signaling pathways. Approximately 30-40% of HCC demonstrate abnormalities in Wnt signaling pathway frequently as β-catenin, Axin1 or Axin2 mutations.[32] In addition, HCV core protein has been shown to promote hepatocyte proliferation driven by accelerated cell cycle progression via upregulation of Wnt-1.[33] Hepatocyte proliferation has also been shown via HCV dysregulation of the EGFR pathway. EGFR has been shown to act as a cofactor for viral entry regulating internalization and membrane fusion.[34] HCV induces EGFR activation and prolongs EGFR signaling through non-structural 5A protein (NS5A) inhibition of EGFR degradation.[35] Aberrations in the EGF gene locus in the form of single nucleotide polymorphisms have been associated with increased HCC risk.[36] HCV has also been shown to upregulate activation of the transcriptional coactivator YAP, which in turn promotes fibrogenesis, and carcinogenesis. To this end, modulation of YAP activation via the Hippo pathway has been shown to reduce HCC risk.[37] Finally, chronic HCV infection induces specific epigenetic changes associated with liver disease progression and carcinogenesis with transcriptional changes that persist after SVR.[38] Epigenetic modifications result in persistent transcriptional changes of postulated HCC risk and

Table 1. Mechanisms of hepatocarcinogenesis after HCV cure

Mechanism	Description
Direct genetic changes	Chronic infection can result in inflammation and oxidative stress causing non-insertional genotoxic events
Virus-induced proliferative and anti-apoptotic signaling	Viral proteins promote and dysregulate multiple growth signaling pathways (e.g. Wnt, EGF, p53, YAP)
Cofactors	Additional oxidative stress due to alcohol, hepatic steatosis, iron, co-infection (e.g. HBV) lead to genomic instability and further activation of growth pathways
Epigenetic changes	HCV-induced epigenetic changes persist after SVR leading to persistent alteration of gene expression

driver genes post-SVR both in patients and in humanized mice associated with increased HCC risk.[38]

Stratification of HCC risk. While DNA-based mutational assays have limited applicability in chronic infection with an RNA virus that does not interact with the host genome, epigenetic and transcriptional alterations after SVR do represent potential biomarkers for HCC risk stratification and targets for risk reduction. A transcriptomic signature derived from hepatic tissue was developed using a 186-gene prognostic liver signature (PLS) and has been shown to be associated with *de novo* HCC, recurrent HCC, and survival.[39,40] Originally derived from patients with advanced HCV disease and HCC, the PLS represents a predictive signature for HCC (and mortality) risk and includes assessment of genes such as EGF known to be dysregulated during HCV infection and has been validated across multiple geographic cohorts and etiologies of liver disease.[41,42] Using paired liver biopsies from patients undergoing both curative and non-curative treatment for HCV, SVR after HCV treatment was shown to be associated with an improved PLS toward low risk; however, the PLS was less reverted in those who developed HCC compared to those who did not develop HCC.[42] Transcriptomic meta-analysis to identify driver genes of HCC risk demonstrate multiple gene modules driving risk, including Wnt, EGF, and YAP related pathways. Informatics on a broad array of transcriptome profiles also identified lysophosphatidic acid (LPA) signaling as a central pathway for HCC; in this regard, LPA antagonism successfully reverses high-risk HCC signature in *ex vivo* cultures of liver tissue.[42]

As promising as transcriptomic signatures (such as PLS) are, their dependence on liver tissue limits their broader clinical application. Non-invasive alternatives are vastly preferred; these may utilize cell free DNA (cfDNA), microRNA, or proteomic or exome profiling for liquid-based evaluation. cfDNA and microRNA have been shown to offer value as a diagnostic biomarker of HCC[43] but may be better suited to early HCC detection as opposed to prognostication and risk stratification. A bioinformatically-derived blood-based prognostic liver secretome (PLSec) using a serum protein-based assay has been developed and, when combined with serum alpha-fetoprotein (AFP), was shown to be associated with both the PLS and long-term HCC risk.[44] Upon development, PLSec was validated in independent cohorts, including patients with advanced fibrosis due to HCV treated with DAA therapy and a cohort with cirrhosis due to mixed etiologies. Development of instruments such as PLSec suggest that long-term HCC risk stratification is feasible and amenable to an individualized precision medicine approach as opposed to universal surveillance. Incorporation of artificial intelligence and genetic polymorphisms into HCC risk prediction represent emerging areas for individualized risk assessment.[45,46] External validation and ongoing evaluation of individualized HCC risk stratification tools is imperative as such instruments become more widely available.[47]

Management of patients with SVR. For patients at elevated risk of HCC, chemoprevention strategies to mitigate future HCC risk have been suggested. Multiple observational studies have demonstrated that coffee consumption may protect against the development of HCC and may be related to changes in serum metabolites induced by coffee consumption.[48,49] Nationwide population studies in patients with chronic viral hepatitis have demonstrated a reduced risk of HCC with either lipophilic statin or aspirin use, suggesting these agents offer chemoprevention benefit.[50,51] Lipophilic statins have been shown to reduce HCC risk signature assessed by PLS in liver tissue. Cell-based studies indicates that lipophilic statins inhibit proliferation through the mevalonate pathway and through inhibition of YAP activation.[37] Randomized controlled trials are underway to assess *in vivo* modulation of HCC risk signatures by lipophilic statins (ClinicalTrials.gov Identifier: NCT05028829). Observational data have also suggested a chemopreventive role for glucose lowering therapy such as metformin against HCC in patients with diabetes.[52] Whether newer class-

es of therapy for diabetes can mitigate the HCC risk remains an open question. As of now, pharmacotherapy for chemoprevention against HCC shows promise but await prospective validation to justify formal adoption in treatment guidelines.

While there may be regression of fibrosis after SVR, an approach to assessment of subsequent fibrosis progression or regression is not well defined. Serial assessment of liver disease severity using non-invasive tools (e.g. FIB-4, elastography, etc.) may assist in management decisions, and in some cases, liver biopsy may be useful. With additional population validation, use of prognostic tools such as PLSec may have a role in stratifying risk and modulating the intensity of HCC surveillance. While some signals for reduced HCC risk have been identified including younger age, lower degree of fibrosis, and absence of prior decompensation,[29] a time to safely discontinue HCC surveillance has not yet been clarified, particularly since late HCC development after SVR is still seen. For those with SVR, since the risk of HCC in the setting of advanced fibrosis and cirrhosis is lowered but not eliminated and a safe-to-stop surveillance signal has not been defined, patients with cured HCV and advanced (F3-4) fibrosis should continue routine HCC surveillance.[53] For these patients, every effort should be made to minimize coexistent risks, including steatosis (when present), alcohol use, optimize glucose control for patients with diabetes, reduce iron levels, and identify and where appropriate treat co-infections such as HBV.

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September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

APASL-AASLD Joint Symposium. A New Area of Interest in Chronic Hepatitis B: To Treat or Not to Treat

Chairs:

Norah Terrault (Univ. of Southern California, USA)
Si Hyun Bae (The Catholic Univ. of Korea, Korea)

Classification and Clinical Characteristics of Gray-Zone in Chronic Hepatitis B

Marc G. Ghany

NIH, USA

Management algorithms have been developed to define which patients with chronic hepatitis B (CHB) should be treated.[1-3] Treatment is recommended for persons at greatest risk for disease progression or outcomes. This can be assessed using HBeAg status, HBV DNA and ALT levels. The three major liver societies vary in their recommendations on who should be treated. Patients who fall into the grey zone classification are ones who do not fulfill criteria for treatment or no treatment. Consequently, the definition of grey zone patients depends on the criteria used to define treatment. For hepatitis B e antigen (HBeAg) positive patients, these represent patients with HBV DNA between 2000-20,000 with either ALT >2X ULN or >ULN and patients with HBV DNA >20,000 with mild ALT elevation based on AASLD and APASL criteria. For HBeAg negative patients, the GZ phenotype includes patients with HBV DNA <2000 with elevated ALT levels and elevated HBV DNA with normal or mildly elevated ALT. The prevalence of grey zone phenotype varies from 28% to 51% depending on criteria used to define phenotype.[4,5] The prevalence is higher among HBeAg negative compared to HBeAg positive CHB, ~80% versus 20%. Prevalence is independent of age, gender, and race.

Patients with a grey zone phenotype represent a heterogenous group with variable HBeAg status, HBV DNA and ALT levels which complicates defining their outcome and management recommendations for treatment. Among North American and European cohorts, during follow-up of 4–8 years, 37%–54% remained grey zone, 44%–85% transitioned to the inactive carrier phase and only a minority, 2%–15% transitioned to HBeAg-negative chronic hepatitis.[6-9] Clinical outcomes are uncommon with low rates of progression to cirrhosis and hepatocellular carcinoma. Contrasting with these generally positive results are data from retrospective cohort studies, involving predominantly Asian patients. These studies highlight that among grey patients 20% to 60% develop HCC and 27% to 70% liver-related deaths over a 10-year follow-up period, suggesting that these patients should be treated.[10,11] However, follow-up has not always been consistent, and some patients would have qualified for treatment; additionally, some were found to have underlying cirrhosis. Studies on liver histology report that a high proportion of patients have significant histological disease. In one study, 73% of grey zone patients who underwent liver biopsy were found to grade 2 inflammation and/or stage 2 fibrosis using the Scheuer classification.[12] Significant liver disease was more frequent among of HBeAg+ compared to HBeAg- grey zone patients.

Determining which patients would benefit from treatment is challenging. Being able to risk stratify patients would be desirable. One study developed a 14-point risk score based on age, male sex, family history of HCC and HBV DNA ≥ 2000 IU/ml to predict HCC. Patients with a high-risk score (score ≥ 8) had a higher cumulative HCC incidence compared to those

with a low-risk score in both untreated and treated patients.[13] Another study used hepatitis B core-related antigen (HBcrAg) to future risk of HCC among grey zone patients. A HBcrAg cutoff of 10,000 U/L was able to stratify patients into low and high risk for HCC.[14] The 10-year HCC cumulative incidence was 0.51% and 5.33% for low and high-risk groups, respectively. Data from this study also showed that antiviral therapy significantly decreased HCC in the high risk but not in the low-risk group. Another study controlling for differences in baseline characteristics reported that antiviral treatment reduced the 10-year rate of HCC from 15% among untreated grey zone patients to 4% among treated patients. A randomized placebo-controlled study of tenofovir disoproxil fumarate was conducted among HBeAg positive and negative grey zone patients with mild disease using changes in liver histology before and after treatment. Antiviral treatment reduced the risk of progression in liver fibrosis (26% in TDF-treated vs 47% in placebo-treated) in patients with chronic hepatitis B and minimally raised ALT, but its effect on necroinflammation was not significant.[15]

Despite these data, given the heterogeneity of patients and clinical outcomes, the decision to treat should be individualized based on presence of risk factors for disease progression and results of non-invasive testing and or liver biopsy. Further management is based on the results of non-invasive testing and or liver biopsy.

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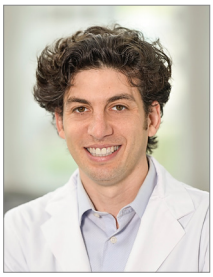
HBeAg-Positive "Gray-Zone": Should We Treat and Why?

Tai-Chung Tseng

National Taiwan Univ., Taiwan

Hepatitis B virus (HBV) is a major driver of hepatocellular carcinoma (HCC). Patients in the early phase of chronic HBV infection are designated "immune-tolerant" due to highly active viral replication without significant liver cell damage. Despite a presumed low HCC risk, recent data present conflicting results, placing immune-tolerant patients in a grey zone of antiviral treatment. Detecting clonally expanded hepatocytes with integrated HBV sequences in immune-tolerant patients suggests a potential HCC risk. However, diverse cohort studies yielded conflicting real-world HCC risk perspectives. Two factors contribute to this disparity. First, current guidelines define patient populations using fluctuating markers like HBV DNA and alanine aminotransferase, potentially misclassifying immune-active patients with transiently normal ALT levels as immune-tolerant patients, necessitating a stable biomarker for accurate classification. Second, hospital-based studies predominantly recruit patients during the antiviral therapy era, underestimating HCC risk due to right censoring introduced by treatment. To address both issues, we recently worked with the REVEAL-HBV study and utilized high serum hepatitis B surface antigen (HBsAg) levels to identify genuine immune-tolerant patients in a cohort study with patients enrolled long before antiviral therapy was available. Over a median of 20-year follow-up, distinct HCC risk trends emerged based on serum HBsAg levels. Patients with high serum HBsAg level (>10,000 IU/mL) exhibited a negligible HCC risk within the first 10 years, challenging initiation of prolonged antiviral therapy due to poor treatment responsiveness in terms of HBeAg seroconversion. Conversely, patients with low serum HBsAg (<10,000 IU/mL) levels were associated with early HCC risk surge, advocating preemptive antiviral intervention. In conclusion, this study underscores the importance of precise patient stratification using a stable biomarker like serum HBsAg, unveiling HCC risk dynamics in so-called "immune-tolerant" individuals. By elucidating HCC development complexities in this special clinical setting, our findings may pave the way for tailored therapeutic strategies based on individualized risk profiles.



HBeAg-Negative "Gray-Zone": Should We Treat and Why?

Jordan Feld

Univ. of Toronto, Canada

Patients with high levels of HBV replication and ongoing hepatitis clearly need antiviral therapy. Patients with very low levels of HBV DNA and normal liver enzymes have little to gain from antiviral therapy with a generally good long-term prognosis. The challenge arises for patients who fall between these two scenarios with either elevated HBV DNA but normal or near-normal ALT or elevated ALT with low level HBV DNA. These patients are often referred to as being in the 'Gray Zone' because they do not quite meet treatment criteria but also do not meet the definitions of those who do not require treatment. How to manage these patients can be challenging in clinical practice.

It is important to distinguish between the 2 types of 'Gray Zone' patients. Those with ALT elevation with undetectable or very low (<2,000 IU/mL) HBV DNA are very unlikely to benefit from antiviral therapy. For these patients, it is critical to explore other reasons for ALT elevation. Related to HBV, this clinical picture is common with HBV/HDV coinfection, and this should always be excluded. However, the ALT elevation may also be unrelated to HBV and due to other comorbid liver diseases, such as Metabolic Associated Steatotic Liver Disease (MASLD) or other chronic liver diseases. These other factors should be explored and provided the HBV DNA remains low, there is likely limited value in antiviral therapy unless the patient has known cirrhosis.

The more challenging scenario is the 'Gray Zone' patient with relatively high HBV DNA (>2,000

IU/mL) but normal or minimally elevated ALT. In this setting, HBV DNA suppression may be of clinical benefit. Large studies have reported that patients with elevated HBV DNA but not meeting standard treatment criteria based on ALT elevation, have a worse prognosis than patients with clearly active disease who received treatment. Furthermore, it is critical to remember that HBV is a dynamic infection, and we are only measuring viral and biochemical parameters at discrete points in time. A normal ALT today may not be a normal ALT 2 weeks ago or 1 month in the future. As such, it is very possible that even if someone does not meet treatment criteria now, they may meet criteria if they were able to be followed more closely. With this concept of missing unrecognized active disease with the potential to lead to progression of liver injury, there is increasing interest in lowering the threshold for treatment initiation to include many of these 'Gray Zone' patients.

Historically, in areas of uncertainty, the 'conservative' approach has been to withhold antiviral therapy. However, many are starting to question this approach. NA therapy is highly effective and long-term studies report a very favourable safety profile. With this in mind and the uncertainty about fluctuating hepatitis in someone in the 'Gray Zone', there is increasing con-

sideration to lower the thresholds for treatment initiation and change the 'conservative' approach to 'when in doubt, treat'. Such an approach may be particularly attractive in resource- limited settings where access to and cost of HBV DNA testing may greatly limit the ability to follow a patient according to standard guidelines.

Optimizing Non-Invasive Methods to Identify Gray-Zone Patients with Liver Fibrosis

Seung Up Kim

Yonsei Univ., Korea

Liver fibrosis is a progressive pathological condition characterized by the excessive accumulation of extracellular matrix in response to chronic liver injury. Accurate and timely detection of liver fibrosis is essential for early intervention and personalized treatment strategies. Noninvasive methods have emerged as attractive alternatives to liver biopsy, which is invasive and associated with potential complications. However, the identification of patients in the gray-zone of liver fibrosis, where the severity is indeterminate, remains a significant challenge. This abstract explores the efforts to optimize noninvasive techniques to better identify gray-zone patients with liver fibrosis.

Noninvasive methods for assessing liver fibrosis can be broadly classified into serum biomarkers, imaging-based approaches, and advanced computational models. Several serum biomarkers, such as FibroTest and Enhanced Liver Fibrosis (ELF) score, have shown promise in distinguishing between fibrosis stages. Nevertheless, their accuracy in the gray-zone remains limited due to overlapping values between adjacent stages. Researchers are actively exploring novel biomarkers and refining existing ones to enhance sensitivity and specificity.

Imaging-based approaches, notably transient elastography (TE) and magnetic resonance elastography (MRE), have gained popularity as noninvasive methods to assess liver fibrosis. These techniques measure liver stiffness, which correlates with fibrosis severity. While they have demonstrated good accuracy in differentiating between significant fibrosis and cirrhosis, their performance in the gray-zone remains suboptimal. Efforts are underway to optimize the cutoff values and incorporate additional imaging parameters to improve diagnostic accuracy.

In recent years, advanced computational models, such as machine learning algorithms, have shown great promise in various medical fields, including liver fibrosis assessment. These models can integrate multiple data sources, including clinical, imaging, and genetic data, to generate predictive models for fibrosis severity. Several studies have demonstrated the potential of machine learning in differentiating between fibrosis stages with improved accuracy compared to traditional methods. However, the complexity and need for large, diverse datasets for training remain challenges in developing robust models for gray-zone identification.

One particular area of interest in optimizing noninvasive methods for gray-zone identification is the combination of multiple approaches. The concept of "biomarker panels" has gained traction, wherein several serum biomarkers are combined with imaging-derived stiffness measurements to enhance diagnostic accuracy. These panels aim to harness the strengths of individual methods and mitigate their limitations. Various studies have shown encouraging results, with improved performance in identifying gray-zone patients when compared to single-method approaches.

Furthermore, the emerging field of "omics" has

opened new avenues for liver fibrosis research. Genomic, proteomic, and metabolomic profiling of patients' samples hold promise in discovering novel biomarkers associated with fibrosis progression. Integrating these omics data with noninvasive methods could lead to more refined and accurate diagnostic tools for gray-zone patients.

In conclusion, optimizing noninvasive methods for identifying gray-zone patients with liver fibrosis is a dynamic and evolving area of research. Improving the accuracy of these methods is crucial for timely and precise clinical management, enabling tailored treatment strategies to prevent disease progression. Combining multiple approaches and integrating novel omics data are promising directions that may unlock new insights and revolutionize the field of liver fibrosis diagnosis and management. Continued collaborative efforts between clinicians, researchers, and industry stakeholders will be essential to realize the full potential of noninvasive methods and improve outcomes for patients with liver fibrosis.

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Symposium 2-7. Debate Session. Strategies to Achieve HBsAg Seroclearance

Chairs:

W. Ray Kim (Stanford Univ., USA)

Maria Buti Ferret (Hospital Universitario Valle Hebron, Spain)

Stopping Antivirals

Wen-Juei Jeng

Chang Gung Univ., Taiwan

Oral antiviral therapy has proved to improve the adverse events of chronic hepatitis B patients including the incidence of cirrhosis, hepatic decompensation and hepatocellular carcinoma. However, since it acts on reverse transcriptase and leads to trivial reduction in HBsAg level during long-term treatment. The major guidelines had proposed finite treatment duration in HBeAg positive chronic hepatitis B (CHB) patients that treatment may be stopped when HBeAg seroconversion with consolidation duration >1 year while no consensus on HBeAg negative CHB patients part. Since it has been estimated to take at least >40 years to achieve functional cure by current oral antiviral agents, it is non-realistic in real-world practice. The life-long treatment brings up the issue of patients' adherence which strongly link to adverse events, loss to follow-up and financial burden in CHB endemic countries. In recent years, growing evidence for the markedly increase functional cure in HBeAg-negative chronic hepatitis B patients receiving finite strategy support the paradigm change from life-long to finite. In this session, we'll review the updated evidence for the benefit of finite strategy, including the increase in HBsAg loss rate and the reduction of liver cancer in cirrhotic population. Moreover, the possible strategy to lower the off-therapy relapse rate, how to predict those may at risk of severe flare or hepatic decompensation whom shall be more closely monitored and how to utilize quantification HBsAg level to differentiate the good flare from bad flare which aids the retreatment decision

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Continuing Antivirals

Jonggi Choi
Ulsan Univ., Korea

Treatment goals for patients with chronic hepatitis B (CHB) is improving quality of life and decreasing liver-related complications. It can be achieved with nucleos(t)ide analogues (NUC), preventing liver failure, decreasing hepatocellular carcinoma (HCC), and with excellent safety.

However, due to the very low rate of on-therapy functional cure, many patients with CHB should continue the NUCs. There has been studies to attempt a finite NUC therapy with a goal of increasing the rate of functional cure probably by enhancing host's immunity. International guidelines mostly recommend to continue NUCs until functional cure is achieved. Recent randomized trials for this finite NUC therapy showed conflicting results. In addition, concerns regarding liver failure or decompensation event by discontinuation of NUC has also should be raised. Too many uncertainties exist in the finite NUC therapy, including the selection of candidate, optimal duration of consolidation period before the cessation of NUC, best biomarkers for predicting functional cure after stopping NUC, and standard for re-treatment strategy. Given the clinical importance of relapse is highly variable, but is especially dangerous in patients with advanced fibrosis or cirrhosis who should not stop NUC therapy, finite NUC therapy should be more carefully approached. Although some patients may undergo HBsAg loss after NUC withdrawal, this occurs in a minority and should not be a stand-alone goal with current long-standing NUC treatment strategy. In addition, Asian patients are potentially less likely to benefit from the finite NUC therapy.

Interferon or Interferon-Based Therapy

Tarik Asselah

Hepatology at Hôpital Beaujon, France

Newer Antiviral Agents: Next Steps to Combination Therapy

Robert G. Gish

Hepatitis B Foundation, USA

Nucleos(t)ide analogues (NUCs) have been the cornerstone of treatment against hepatitis B virus (HBV) for decades however, NUCs have no direct effect on the HBV transcriptional template (ie, covalently closed circular DNA [cccDNA]) and so functional cure is rarely achieved, and we are not able to approach a sterilizing cure or complete cure. Over recent years, there has been a significant improvement in our understanding of the viral life cycle with a focus on cccDNA. Knowing this information: what is they dynamic of cccDNA as functional cure evolves?

- Given the pleotropic nature of HBV persistence, it is likely that a combination of immunomodulators, drugs that focus on cccDNA, as well as direct-acting antivirals (DAAs) will be required to achieve the highest rates of functional cure, sterilizing cure, and complete cure.
- The heterogeneity of clinical outcomes may demand a personalised approach to pharmacotherapy and predictive biomarkers that evaluate drugs in development and with a focus on cccDNA and its transcripts.
- Knowing the dynamics of cccDNA during the functional cure event will help with drug development as well as direct patient management.

Elimination of the HBV will be challenging due to integration of its genetic material into host DNA and most importantly the formation of a transcriptional template (cccDNA) in 18-21 different forms. cccDNA is resistant to host endonuclease enzymes and thus we will need a much more targeted approach to this component of the viral life cycle.

The World Health Organisation have targeted a 90% reduction in the incidence of viral hepatitis by the year 2030. Achieving this ambitious goal will require the expansion of screening programmes, improved linkage to care, and a broader repertoire of therapeutic options including medications that focus directly or indirectly on cccDNA.

After cellular entry and following disassembly of its nucleocapsid, relaxed circular DNA (rcDNA) is transported to the nucleus and converted into cccDNA by a series of host enzymes; this episomal structure is inherently stable and forms the template for pre-genomic RNA (pgRNA, 3.5kb) and subgenomic RNA expression (2.4kb, 2.1kb, 0.7kb). Transcriptional activity fluctuates during the course of infection and is influenced by viral proteins (core, HBx), host transcriptional factors (Smc5/6), and epigenetic modifiers (eg, histone acetylation).

The multi-functional HBV polymerase is responsible for the encapsidation of pgRNA, synthesis of the minus and positive DNA strands, and degradation of the RNA template. Early in the viral life cycle, nucleocapsids containing newly synthesised rcDNA are transported back to the nucleus and amplify the cccDNA reservoir thus blocking encapsidation, which may prevent cccDNA regeneration. During reverse transcription of rcDNA into cccDNA, primer translocation

may fail to occur, and this leads to the formation of double-stranded linear DNA (dslDNA). The structure integrates into the host genome at the site of DNA breaks and is an additional source of subgenomic RNA transcripts thus blocking cccDNA levels this activity may prevent further viral integration.

All 3 agents first line agents (ETV, TAF and TDF) are orally administered, well tolerated, and reduce the risk of liver-related complications; however, they have no direct effect on cccDNA transcriptional activity and so functional cure is seldom achieved. When functional cure is seen, even though rare, those patients have a decrease of cccDNA from their liver cells and possibly clearance in a few patients. Interferons, an alternate to NUCS, stimulate an array of interferon-stimulated gene (ISG) products, and these have broad suppressive effects on HBV activity. Interferon-α (IFN-α increases cytidine deaminase activity (APOBEC3) and triggers G-to-A hypermutation throughout the viral genome. In addition, it promotes the degradation of pgRNA, impedes HBV-RNA nuclear export, and recruits transcriptional co-repressors to cccDNA; this may explain the HBsAg clearance seen in a subset of patients with HBsAg loss.

Direct targeting of cccDNA

Achieving sterilizing cure requires the silencing and/or elimination of the cccDNA transcriptional template however, this is challenging due to its super-coiled structure and resistance to host endonucleases. In recent years, there has been growing interest in genome editing techniques, including zinc-finger nucleases (ZFNs), transcription activator-like endonucleases (TALENs), and the clustered regularly interspaced short palindromic repeats (CRISPR/Cas) system, but none of these have made it to the clinic yet. In the latter tool, Cas9 proteins are directed to target sequences by guide RNA molecules, triggering double-stranded DNA breaks and the insertion of mutagenic indels by recombination (NHEJ) mechanism. This process requires a protospacer- adjacent motif within target DNA sites that is typically 2-6 nucleotides in length. In vitro studies have been promising, suggesting that engineered CRISPR/Cas systems can cause a dramatic reduction in cccDNA levels however, concerns remain about the optimal delivery systems, fate of mutated cccDNA variants, and potential for genome wide off-target effects. Other approaches to silencing cccDNA activity include base editing, epigenetic modifications, and interference with transcriptional co-factors/co-repressors (eg, HBx, FXR-α). Newer DAA therapies are summarized in my separate abstract.

The World Health Organization has targeted the "elimination" of HBV as a global health problem by the year 2030. As we strive to achieve higher rates of functional cure, a pillar of this new combination therapy will be a focus on cccDNA directly or indirectly and to adopt a personalised approach to pharmacotherapy and use predictive biomarkers such as quantitative RNA and fine needle aspirates to directly look into the liver cell to determine target effects.

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DAY 2 | Friday, Sept. 22, 2023

Symposium 2-2. Update of Cirrhosis and Portal Hypertension

Chairs:

Shiv Kumar Sarin (Institute of Liver & Biliary Sciences, India)
Dong Joon Kim (Hallym Univ., Korea)

Liver and Spleen Stiffness for the Estimation of Portal Hypertension and Cirrhotic Complications

Moonyoung Kim

Yonsei Univ. Wonju, Korea

HVPG measurement is the gold standard for the evaluation of portal hypertension (PH) not only in research but also in clinical practice. An HVPG of ≤5 mmHg is normal, whereas a value of >5 mmHg is diagnostic for PH. An HVPG of ≥10 mmHg is diagnosed as clinically significant portal hypertension (CSPH), which has a risk of clinical decompensation (i.e., ascites, variceal bleeding, and hepatic encephalopathy) and hepatocellular carcinoma (HCC). The risk of variceal rupture increases when the HVPG is ≥12 mmHg. An HVPG of ≥16 mmHg increases the risk of mortality, and an HVPG of ≥20 mmHg increases the risks of failed variceal bleeding treatment and mortality.

Recently, new concept, compensated advanced chronic liver disease (cACLD) has been proposed to show that severe fibrosis and cirrhosis are a continuum in asymptomatic patients, and that determining the difference between the two stages is often clinically impossible. Portal hypertension may occur before an established histological diagnosis of cirrhosis. So, early diagnosis of cACLD and clinically significant portal hypertension (CSPH) is important to prevent the progression to advanced decompensated state.

Among non-invasive test, vibration-controlled transient elastography (VCTE, Fibroscan®) is useful and allows the early identification of patients with CLD at risk of developing CSPH. Liver stiffness (LS) measurement by VCTE can suggest cACLD in asymptomatic subjects with chronic liver disease. Good correlation has been reported between HVPG and LS by VCTE, especially in HVPG values less than 10 mmHg. LS can discriminate the presence of CSPH. LS by VCTE values >13.6 kPa or LS >21 kPa have been found to have a 90% sensitivity and a 90% specificity for the diagnosis of CSPH. The Baveno VI Consensus Conference recommended that a LS by VCTE of 21 kPa or more be used to indicate CSPH. In addition, LS by VCTE stiffness <20 kPa and with a platelet count >150.000 have a very low risk of having oesophageal varices that require therapy. These patients do not need endoscopic screening. Twenty-one percent of endoscopies could be avoided with these criteria and fewer than 5% of patients with varices would be missed.

Spleen stiffness (SS) measurement is another attractive approach. It does not only reflect static hepatic resistance secondary to liver fibrosis but may also capture dynamic presinusoidal vasoconstriction, congestion of the portal blood inflow, and PH induced splenic fibrosis. SS is a prognostic indicator of liver-related events and correlates well with HVPG. A cutoff value of 41–46 kPa for SS had been useful for identifying high-risk varices and CSPH.

Recently, researches of magnetic resonance elastography (MRE) for the assessment of liver fibrosis and portal hypertension have increased. LS and, especially, SS obtained by MRE showed a positive correlation with HVPG. A criterion of MRE LSM <4.2 kPa plus platelet count >180 × 10^3 /μL showed a negative predictive value of 100% for the presence of esophagogastric varices. At present, MRE is not universally applied in

clinical practice and is an expensive modality. Further studies are needed to accumulate evidence on the value of MRE as a noninvasive alternative to invasive HVPG for evaluating PH and predicting PH related complications. In the future, the use of MRE will be established and widespread.

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Antiviral Therapy and the Outcome of Patients with Decompensated Cirrhosis

Sung-Eun Kim

Hallym Univ., Korea

Cirrhotic patients with chronic hepatitis B and/or chronic hepatitis C may continue to progress liver disease and it may lead decompensation of liver cirrhosis or hepatocellular carcinoma (HCC), especially in those with active viral replication. Decompensation of liver cirrhosis define as presentation of jaundice, ascites, variceal bleeding or hepatic encephalopathy. Earlier studies have demonstrated that the prognosis of decompensated cirrhosis is usually poor with a 5-year survival rate at 14-35% under conventional standard of care. The approval of oral antiviral agents has greatly improved the prognosis, as demonstrated in several cohort studies and randomized clinical trials involving therapy with nucleos(t)ide in chronic hepatitis B and direct acting agents in chronic hepatitis C. These antiviral agents are effective in restoring liver function and improving survival in patients with decompensated cirrhosis especially if antiviral treatment is initiated early enough. Some patients present recompensation of decompensated cirrhosis. At present, there are limited research data on the recompensation of decompensated viral cirrhosis. Recompensation is being treated with important concepts, there is still controversy regarding the evaluation time, evaluation indicators, influencing factors, and long-term prognosis of recompensation.

Optimal Assessment and Improving Survival in Acute Variceal Bleeding

Shiv Kumar Sarin

Institute of Liver & Biliary Sciences, India

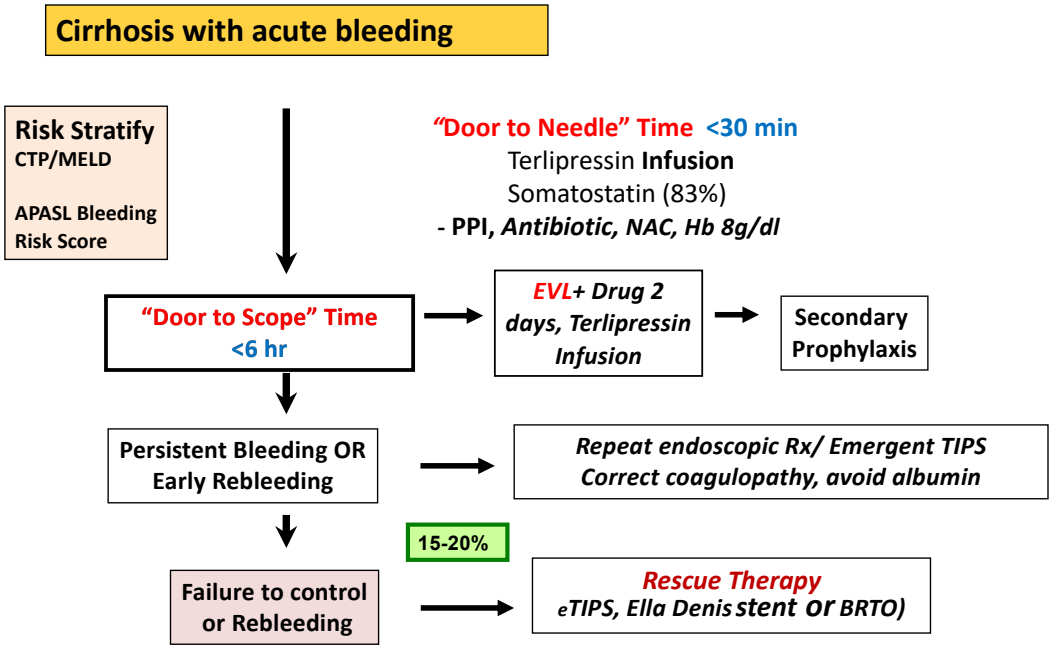
Acute variceal bleeding (AVB) is a medical emergency and associated with a mortality of 20 to 40% at 6 weeks and is defined as presence of hematemesis within last 24hr of presentation, and / or ongoing melena, with last melenic stool within last 24hr. Patient should be stratified and risk assessment done based on the Child status and MELD score of the patient. Also, if the patient has acute-on- chronic liver failure, concomitant renal failure or sepsis, extra care in the GI bleed ICU should be done.

Vasoactive therapy- Terlipressin, somatostatin or octreotide, should be given immediately (<30min of hospitalization, 'Door to Needle Time') combined with endoscopic variceal ligation (EVL) ('Door to Scope Time' <6 hrs). Combination therapy is effective in about 80-85% patients. Failure to control bleeding is defined as fresh hematemesis with in 2 hr of combination of vasoactive drugs + EVL, >2 g drop in Hb (6% drop in Hct) without transfusion and hemodynamic instability. This failure, is considered as refractory variceal bleeding and requires immediate change in therapy. Half transfuse the amount of blood loss, to prevent rebleeding. There is no advantage of infusion of plasma or clotting factors, Predictors of failure to control bleeding include high hepatic venous pressure gradient (HVPG) >20 mmHg, active variceal spurter, infection, high MELD and portal vein thrombosis. Patients not responding to the combination therapy should undergo early emergency TIPS, specially if the HVPG is >20 mmHg, even in patients with advanced liver disease. Patients with uncontrolled bleeding have better survival with emergent TIPS done within 8 hours than beyond 8 hours. According to the recent Baveno VII guidelines, high baseline MELD is not a contraindication, but patients with CTP of 14 or more should not be considered. TElla Danis stent, a self expanding metal stent should be considered in such patients. These stents are quite effective in controlling post- EVL ulcer bleed and can be removed easily after a week or two.

Antibiotic prophylaxis is recommended and search for acute ischemic hepatic injury should be done. Ischemic hepatitis (IH) develops in about 10% of cirrhotics following AVB more so in Child's C patients and is associated with higher mortality. N acetyl cysteine (NAC) therapy in a recent study at ILBS has shown to significantly ameliorate the development of severe IH and decrease the incidence of AKI, though it was not found to reduce mortality.

Gastric varices are present in about 20% of patients with portal hypertension with a reported incidence of bleeding of about 25% in 2 years, with a higher bleeding incidence for IGV1 and GOV2. High risk varices are >20mm, Child class (C>B>A), and endoscopic presence of variceal red spots. Use of N- butyl-cyanoacrylate glue with or without EUS guided coil embolization is treatment of choice. Balloon retrograde obliteration of varices (BRTO) and TIPS can be used in patients with failure to control GV bleed. A team approach and a dedicated GI bleed ICU help improve patient outcomes.

Acute Variceal Bleed: Management 2023



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The Role of Antibiotic Therapy in Acute Decompensation

Jung Gil Park

Yeungnam Univ., Korea

Bacterial infections are a significant complication of cirrhosis, and they are linked to a high mortality rate.[1] These infections can either trigger the onset of decompensation, such as variceal hemorrhage or hepatic encephalopathy, or worsen the condition in patients who are already decompensated, leading to issues like variceal rebleeding or hepatorenal syndrome. Importantly, infections are a major factor contributing to acute-on-chronic liver failure in Western countries, and they can even occur in patients with compensated cirrhosis.[2] Consequently, bacterial infections are associated with a considerably higher risk of in-hospital mortality, ranging from four to five times higher, and an increased risk of death due to sepsis, which is twice as likely.[3]

Given these risks, it is imperative to take measures to prevent infections in individuals with cirrhosis. The primary approach currently employed is the use of prophylactic antibiotics. This presentation discusses the advantages and disadvantages of using prophylactic antibiotics, identifies the specific subpopulation of cirrhosis patients for whom they are recommended, and outlines strategies aimed at preventing infections while minimizing the development of antibiotic resistance in cirrhosis patients.

Antibiotic prophylaxis in patients with cirrhosis has been associated with a decrease in the incidence of bacterial infections. The three clinical settings in which there is evidence that antibiotic prophylaxis prevents infections are specified below and are summarized in table 1.[4]

There are several concerns associated with antibiotics use. The most serious one is development of antibiotics resistance. Across Europe, North America, and Asia, studies have shown that approximately 11% to

Table 1. Indication of prophylactic antibiotics in cirrhosis

Indication	Antibiotic and dose	Duration
Gastrointestinal bleeding	Norfloxacin 400 mg/12 h PO IV ceftriaxone 1 g/d in patients with advanced cirrhosis (at least 2 of the following: ascites, jaundice, hepatic encephalopathy, and malnutrition)	Seven days
Primary prophylaxis in patients with low protein ascites (<15 g/L)	Norfloxacin 400 mg/d PO in patients with advanced cirrhosis: - Child-Pugh score ≥9 points with serum bilirubin ≥3mg/dl and/or - Impaired renal function (serum creatinine ≥1.2mg/dl, BUN ≥25 mg/dl or serum Na ≤130 mEq/L	Not specified
Secondary prophylaxis of SBP	Norfloxacin 400 mg/d PO Bactrim DS PO daily or 5 days/week Ciprofloxacin 500 mg PO daily	Not specified

45% of patients with spontaneous bacterial peritonitis (SBP) were infected with microorganisms that are resistant to first-line third-generation cephalosporin antibiotics.[5] These high rates of antibiotic resistance are closely linked to recent and frequent use of antibiotics. Other factors that contribute to the development of antibiotic resistance in cirrhosis patients include acquiring the infection in a healthcare setting (nosocomial acquisition) and having recently been infected with a multi-drug resistant (MDR) organism. Furthermore, it's crucial to note that antibiotic use has been identified as the most significant predictor of invasive fungal infections following liver transplantation, with a troubling case fatality rate of 60%. Infections caused by MDR organisms are associated with an elevated risk of severe complications such as septic shock, acute kidney injury, and even death, both before and after liver transplantation. Clostridium difficile infection is another concern in cirrhosis. It is linked to increased rates of hospitalizations and healthcare expenses, along with a notably elevated mortality risk (1.6 times higher compared to individuals without C. difficile infection). One of the primary factors contributing to C. difficile infection in cirrhosis is the use of antibiotics during hospitalization, with an adjusted odds ratio indicating that patients who receive inpatient antibiotics face a twelvefold increase in their risk of developing C. difficile infection.[6] Additionally, direct toxicities associated with antibiotics and drug-drug interactions are potential concerns in cirrhosis.

In summary, bacterial infections in cirrhosis are a serious concern, with high mortality rates. Prophylactic antibiotics have proven effective in some cases, but their use carries risks like antibiotic resistance. Balancing these factors and implementing targeted prevention strategies are essential for improving outcomes in cirrhosis patients.

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APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Symposium 2-3. Non-B and Non-C Viral Hepatitis: Pathogenesis and Treatment

Chairs:

Jaeseok Hwang (Keimyung Univ., Korea)
Hee Bok Chae (Chungbuk National Univ., Korea)

Immunopathogenesis of Acute Hepatitis A

Eui-Cheol Shin

KAIST, Korea

The clinical manifestations of hepatitis A virus (HAV) infection range from asymptomatic infection to acute liver failure.[1] Risk factors for severe acute hepatitis A are older age (>40 years) and pre-existing liver disease.[2] Liver injury during hepatitis A is not directly caused by HAV but is known to be caused by immune-mediated mechanisms. Patients with acute HAV infection exhibit bystander activation of memory $CD8^+$ T cells.[3] Independently of TCR stimulation, elevated IL-15 was found to be the major driver of bystander activation during acute HAV infection. Bystander-activated $CD8^+$ T cells recognized target cells and exerted innate-like cytotoxicity in a manner dependent on NKG2D or NKp30. Moreover, the innate-like cytotoxicity of bystander-activated $CD8^+$ T cells was significantly correlated with the level of ALT in serum during acute HAV infection. These results demonstrated a pathological role of bystander-activated memory $CD8^+$ T cells during acute HAV infection. In addition, IL-15-induced CCR5 upregulation is involved in the migration of bystander-activated $CD8^+$ T cells that contribute to liver injury during acute HAV infection.[4] The finding that IL-15-activated bystander memory $CD8^+$ T cells are involved in liver injury during acute HAV infection explains why HAV infections lead to different clinical outcomes depending on the age of the patient.[5]

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Novel Therapies for Hepatitis D Virus

Young Eun Chon

CHA Univ., Korea

Hepatitis D virus (HDV) is the smallest virus known to infect animals. The HDV genome is small consisting of approximately 1700 nucleotides, circular single stranded, and negative-sense RNA. HDV is a defective RNA virus that does not encode its own envelope proteins, enters the liver through HBsAg-expressing hepatocytes. Delta antigen has two forms, small and large delta antigen. The viral genome and the delta antigen proteins are encapsulated within a lipid envelope that is embedded with the full complement of HBV surface antigen proteins. Treatment of chronic hepatitis D is based on blocking each stage of the life cycle of the HDV.

The current standard treatment for HDV is a 48-week course of weekly subcutaneous injections of pegylated interferon alpha (pegIFNα) which suppresses HDV replication in approximately 20%–30% of the patients 24 weeks off therapy, which induce significant side effects. Bulevirtide (BLV), a drug in phase III study, is an entry inhibitor for HDV, which competitively acts on sodium taurocholate cotransporting polypeptide (NTCP), an entry receptor shared by hepatitis B virus (HBV) and HDV viruses. In 2020, BLV was first approved by European Medicine Agency in patients with compensated liver disease and positive HDV RNA with or without nucleotide anaglogues. According to the ongoing phase 3 study, BLV treatment for 24 weeks resulted in significant decrease in HDV RNA and ALT. Virologic response (undetectable HDV RNA or ≥2 log10 IU/mL decrease from baseline) in patients with no treatment, BLV 2 mg, and BLV 10 mg was 4%, 55%, and 68%, respectively. Another drug in phase III study is lonafarnib, an oral prenylation inhibitor that reduces HDV virus load by blocking prenylation, a process involved in virus assembly, replication, and subsequent hepatocyte infectivity. Virologic responses (undetectable HDV RNA or ≥2 log10 IU/mL decrease from baseline) at the end of treatment were reached in 46% and 89% of patients receiving the all-oral regimen of lonafarnib 50 mg bid + ritonavir, and combination regimen of lonafarnib (25 or 50 mg bid) + ritonavir + peginterferon peginterferon alpha, respectively. Pegylated interferon lambda (PEG-IFN-lambda) stimulates cell-mediated immune responses during viral infections. PEG-IFN lambda binds to type III IFN receptors which are mainly expressed in hepatocytes and to a lesser extend in hematopoietic and central nervous system cells. Therefore, typical side effects of IFN-α treatment are not expected with PEG-IFN-lambda treatment. In a phase II study evaluating the safety, tolerability, and efficacy of PEG-IFN-lambda in cheonic hepatitis D, 33 patients were randomized to receive either 120 μg or 180 μg subcutaneously for 48 weeks followed by a 24-week observation period. At the end of treatment, the primary end point (>2 log HDV RNA decline or HDV RNA negativity) occurred more frequently in patients treated with PEG-IFN-lambda 180 μg than 120 μg (7/14 vs. 4/19). Five of the 14 patients (36%) treated with PEG-IFNlambda 180 μg remained HDV RNA negative after 24 weeks of follow-up. Nucleic acid polymers (NAPs) inhibit the

assembly and release of HBsAg coated viral particles and are therefore considered as an additional antiviral treatment of HDV infection. In a clinical trial including 12 patients treated with IV 500 mg of REP 2139 once weekly for 15 weeks followed by 15 weeks of 250 mg REP 2139 in combination with PEG-IFN-α followed by PEG-IFN-α monotherapy for 33 weeks, 9 of 12 patients showed RNA negativity at end of treatment. In the extended data for REP 301, status of 7 among 11 patients with HDV RNA undetectable and normal liver function was maintained after 3.5 years. RNA interference compounds (RNAi) are short RNA molecules targeting the transcripts of viral RNA. JNJ-3989 silences all transcripts deriving from HBV cccDNA and integrated viral DNA. Currently, there is data of only HBV monoinfected patients (n=84), and HBsAg reduction >1 log10IU/mL was noted in 97.5% of patients. A phase II study to evaluate the safety and efficacy of JNJ-3989 in HBV and HBV co-infection is currently ongoing.

Disease Burden and Potential Therapeutic Approach to HEV Infection

Lubna Kamani

Liaquat National Hospital, Pakistan

Hepatitis E (HEV) is a single stranded positive strand RNA virus and belongs to family Hepeviridae. The most studied specie that effects human is Orthohepevirus and it is further divided into 8 genotypes.[1] HEV genotypes 1 and 2 are exclusively found in human's, mainly in developing countries of Asia and Africa and are responsible for outbreaks and epidemics. Genotypes 3 and 4 are zoonotic with various animal hosts like pig, deer, rabbit, goat leading to sporadic cases in developed western countries and China.[2] Genotypes 5 and 6 are mainly isolated in wild boars whereas genotype 7 and 8 are mainly found in camels. Transmission is mainly via fecal-oral route and poor sanitation, genotypes 3 and 4 are often transmitted by consuming contaminated and undercooked animal products. Sporadic cases of HEV infection transmitted through blood transfusion[3] and organ donation are widely reported in literature leading to acute and chronic HEV infection in immunosuppressed patients.[4]

It is estimated around 20 million people are infected with HEV globally and >3million symptomatic cases. HEV infection is generally an acute, self-limiting illness with mortality ranges form 0.5-3% in young adults. However, it can be chronic in immunocompromised patients with high mortality in pregnant women.[5] Apart from acute hepatitis there are various extra-hepatic manifestations reportedly including renal, nervous system, thyroid, hematological disorders and cardiac, their mechanisms, pathological relations and treatment needs to be explored further through research.[6]

Incubation period of HEV varies around 15-60 days. Mostly, acute phase of infection shows positive anti-HEV IgM and HEV RNA with or without development of anti-HEV IgG. Presence of only anti-HEV IgG represents past infection. Persistence of HEV RNA beyond 3 months denotes chronic infection.[7]

In the absence of effective treatment, prevention is the key. Adequate sanitation with consumption of properly cooked food disrupts the transmission route. In 2011 HEV vaccine (HEV239, Hecolin) made available in China and some other nearby Asian countries (not FDA approved yet). It has shown 100% protection against genotype 1 and some cross protection against genotype 4 when total of three doses are administered. Safety data regarding its usage in immunosuppressed patients and pregnant ladies is still lacking.[8] No drug is FDA approved for HEV treatment. Treatment is rarely required as most of the patients get better with conservative management. Peg INFα and ribavirin are the most used medication in severe cases of HEV. Ribavirin remains ineffective in 20 % of patients because of mutations in HEV genome and Peg INFα can be administrated only for the subset of liver-transplant recipients but cannot be used after other organ transplantation.[9] HEV is a major health concern globally. Advanced research is needed regarding understanding of its pathogenic mechanism and transmission route. Evaluation of newer therapies

and availability of effective and safe vaccine is urgently warranted.

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Pathogenesis and Management of Non-Hepatotropic Viruses

Ju-Yeon Cho

Chosun Univ., Korea

The clinical spectrum of viral hepatitis is vast but most discussions are often restricted to hepatotropic viral infections (Hepatitis A to E) as they are the most prevalent. However, the WHO reported an outbreak of 1,010 probable cases of severe acute hepatitis of unknown etiology in children as of July 2022. In such cases, clinicians strive to search for the cause in these non-hepatotropic viruses. Although the exact etiology is yet to be reveled non-hepatotropic viruses are highly suspected as the culprit.

Acute hepatitis caused by non-hepatotropic viruses is usually a component of the severe phenotype of the viral infection, resulting from immune-mediated injury or direct viral infection. Most of the cases identified of a non-hepatotropic viral infection are through clinical suspicion in patients with hepatitis. Yet, there are no current guidelines to manage patients suspected of viral hepatitis secondary to non-hepatotropic viral infection, a gap that needs to be addressed. The pathogenesis and management of non-hepatotropic viral hepatitis will be emphasized in this session to assist clinicians.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Symposium 2-5. Metabolic Disease and Viral Hepatitis

Chairs:

Jose D. Sollano (The Univ. of Santo Tomas, Philippines)
Oh Sang Kwon (Gachon Univ., Korea)
Sang Hoon Park (Hallym Univ., Korea)

Role of Metabolic Risk Factors in the Outcome of Viral Hepatitis

Lai Wei

Tsinghua Univ., China

Hepatitis B virus (HBV) infection and nonalcoholic fatty liver disease (NAFLD) are two major causes of chronic liver disease (CLD) that can cause liver cirrhosis and hepatocellular carcinoma (HCC). It is a trend to superimpose NAFLD on chronic HBV infection in Asia. This review presents the epidemiology of concurrent NAFLD in chronic hepatitis B (CHB) patients and focuses on the impact of concurrent NAFLD on the outcome of CHB patients in Asia. Although CHB patients tend to have lower prevalence and incidence of NAFLD than the general population, concurrent NAFLD among CHB patients is still common and has an upward trend over time. Concurrent NAFLD can promote hepatitis B surface antigen (HBsAg) seroclearance, might inhibit HBV replication but exacerbate liver fibrosis. The impacts of concurrent NAFLD on HCC risk, all-cause mortality, and antiviral treatment response in CHB patients remain controversial.

Effects of Alcohol Drinking on the Prognosis of Patients with Viral Hepatitis

Won Kim

Seoul National Univ., Korea

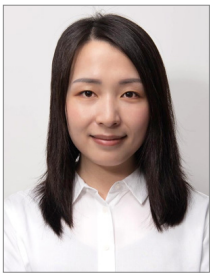
Alcohol consumption can have a significant impact on the outcome of chronic viral hepatitis, which is an inflammation of the liver caused by viral infections. Among several different types of viral hepatitis, the relationship between alcohol consumption and the outcome of viral hepatitis is most studied in the context of hepatitis B and hepatitis C. The impact of alcohol can vary depending on the extent of liver damage, the type of viral hepatitis, and other individual factors. In this topic, I will review how alcohol can affect these conditions.

Chronic alcohol consumption can negatively affect the course of chronic hepatitis B. It can lead to an increased risk of developing cirrhosis and hepatocellular carcinoma (HCC) in individuals who are already infected with HBV. Alcohol-induced liver damage can also impair the immune response, making it harder for the body to clear the virus. Additionally, some antiviral medications used to treat chronic hepatitis B may have interactions with alcohol, reducing their effectiveness.

Alcohol consumption is a well-established risk factor for the progression of hepatitis C. People who drink alcohol and have HCV infection are more likely to develop liver fibrosis and cirrhosis. Alcohol can accelerate the progression of liver damage caused by HCV and increase the risk of liver-related complications. Individuals with chronic HCV infection are usually advised to avoid alcohol completely, as it can hinder the effectiveness of antiviral treatments and increase the likelihood of adverse outcomes.

Overall, alcohol and viral hepatitis create a synergistic effect that significantly increases the risk of liver damage and disease progression. Alcohol consumption can exacerbate the inflammation and damage caused by the hepatitis virus, and it can also impair the liver's ability to regenerate and heal. This can lead to more severe liver diseases, including cirrhosis and HCC.

Given these risks, individuals with viral hepatitis, especially those with chronic infections, are generally advised to avoid alcohol completely or limit their alcohol consumption to the lowest possible levels.



MAFLD in Chronic Hepatitis B: Friend or Foe?

Lung-Yi Mak

The Univ. of Hong Kong, Hong Kong

Chronic hepatitis B (CHB) infection and non-alcoholic fatty liver disease (NAFLD), or recently renamed as metabolic-associated steatotic liver disease (MASLD), are both major etiologies of cirrhosis and HCC. CHB affects 292 million worldwide; a large majority of HCCs in Asia are attributable to CHB. NAFLD, which affects approximately 25% of the global population, is already the fastest rising etiology of cirrhosis and HCC in the United States, France, and the United Kingdom; and the overall prevalence reaches approximately 30% in Asia. The incidence of hepatic steatosis in HBV-endemic regions is similarly high, indicating that the two diseases.

coexist in a considerable number of patients. At present, data on the impact of concomitant steatosis on the natural history of CHB remain conflicting. Hepatic steatosis appears to be associated with lower viral burden in CHB, and earlier age of achieving hepatitis B surface antigen seroclearance. While some studies reported a paradoxically lower risk of developing adverse hepatic outcomes (e.g., HCC) among patients with CHB and hepatic steatosis, others reported higher risk of disease progression. There is a significant knowledge gap in understanding the mechanisms behind these observations

Management Strategies for Viral Hepatitis with Concurrent MAFLD

Hye Won Lee

Yonsei Univ., Korea

The prevalence of metabolic syndrome is rising as the age of chronic hepatitis B (CHB) sufferers increases. In 2020, the concept of metabolic dysfunction-associated fatty liver disease (MAFLD) was introduced, encompassing patients with chronic viral hepatitis, excessive alcohol consumption, drug-induced steatosis, and other chronic liver diseases. MAFLD is diagnosed when hepatic steatosis is accompanied by one of the following: overweight or obesity, diabetes mellitus (DM), or two metabolic risk factors.

Patients with CHB and MAFLD should be monitored regularly for viral activity and steatosis. Although liver biopsy is considered the gold standard for diagnosing and assessing the severity of hepatic steatosis, its use as a monitoring tool for this condition remains limited. Therefore, there is a need for a simple, non-invasive test to assess steatosis progression in CHB patients undergoing surveillance every 6 months. The controlled attenuation parameter (CAP), as determined by transient elastogrpahy, is commonly used in clinical practice. In a study involving 366 treatment-naive CHB patients who underwent liver biopsy, CAP demonstrated greater accuracy in the assessment of steatosis compared to the hepatic steatosis index and ultrasonography. Further studies are needed to establish the effectiveness of CAP in CHB patients to identify individuals at high risk for nonalcoholic fatty liver disease.

Although a negative correlation was observed between steatosis and hepatitis B virus (HBV) activity, this relationship remains controversial. CHB patients with steatosis exhibit lower viral activity, as reflected in lower hepatitis B e antigen positivity and HBV DNA levels compared to those without steatosis. However, steatosis and HBV activity are factors for fibrosis progression and the development of hepatocellular carcinoma (HCC). Aggressive treatment strategies, including earlier initiation of antiviral therapy according to liver enzyme levels, should be considered for CHB patients with MAFLD. Additionally, lifestyle modifications play a crucial role in the management of MAFLD patients, weight reduction serves as both a goal and an indicator of intervention effectiveness. Individualized management strategies for poor responders include serial monitoring of viral activity and aspartate aminotransferase or alanine aminotransferase levels.

Factors related to metabolic dysfunction play a pivotal role in the development of fatty liver disease. Central obesity, DM, hypertension, and dyslipidemia are recognized as risk factors for fibrosis and the development of HCC. These metabolic risk factors can contribute independently to fibrosis and HCC, regardless of their impact on HBV activity. In a study involving 663 treatment-naive CHB patients who underwent liver stiffness measurement, significant associations were observed between fibrosis progression and metabolic syndrome, central obesity, and low levels of high-density lipoprotein cholesterol, irrespective of changes in alanine aminotransferase levels and viral load. Moreover, significant associations were observed between

DM and factors predictive of HCC development in patients receiving potent antiviral treatment. Therefore, addressing metabolic dysfunction is essential to improve the prognosis of CHB patients with MAFLD.

In conclusion, individualized monitoring using appropriate tools and intervals is essential for CHB patients with MAFLD. Furthermore, aggressive and comprehensive strategies to address viral activity, steatosis, and metabolic disorders can significantly enhance the long-term prognosis of CHB patients with MAFLD.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Symposium 2-6. Prevention and Surveillance of Viral Hepatitis-Associated HCC

Chairs:

Shuichiro Shiina (Juntendo Univ., Japan)
Joong-Won Park (National Cancer Center, Korea)
Jong Young Choi (The Catholic Univ. of Korea, Korea)

Anti-HBV Therapy to Prevent HBV-Associated HCC

Tetsuya Hosaka

Toranomon Hospital, Japan

Over the past 15 years, nucleos(t)ide analogues (NUC) treatment, including entecavir (ETV) and tenofovir (TDF or TAF), have been approved and were successful in suppressing circulating serum viral loads for chronic hepatitis B patients (CHB). ETV, TDF and TAF are potent compounds that has proved effectiveness in suppressing HBV DNA replications with minimal drug resistance. Some previous studies indicated that long-term viral suppression by NUC treatment could lead to reduce the risk of hepatocellular carcinoma (HCC), but the HCC risk could not be completely eliminated by NUC treatment.[1-3] There are some risk factors including cirrhosis and viral factors regarding the HCC development in patients treated with long-term NUC.[4]

This presentation will review the risk reduction of HCC by long-term NUC treatment and these risk factors.

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Anti-HCV Therapy to Prevent HCV-Associated HCC

Do Young Kim

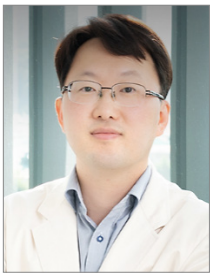
Yonsei Univ., Korea

In spite of more than 2 decades of research efforts, the pathogenesis of hepatitis C virus (HCV)-induced hepatocellular carcinoma (HCC) and the HCC risk after antiviral cure are still incomplete understood. Several meta-analyses that included studies reporting that a sustained virological response (SVR) to interferon (IFN)-based therapy for chronic hepatitis C is an indicator of the risk of HCC occurrence. In a study, it was reported that approximately 60% of IFN-SVR patients died from non-liver-related disease, while approximately 35% of non-IFN died from non-liver-related diseases. In a Korean retrospective study, a total of 463 chronic hepatitis C patients who underwent pegylated interferon alfa and ribavirin therapy were classified as SVR or non-SVR based on response to antiviral therapy. Three hundred patients achieved SVR, and 163 were classified into the non-SVR group. The overall SVR rates were 64.8%, and during a median follow-up of 36.1 months, non-cirrhotic patients with SVR had significantly lower risk of progression to cirrhosis compared with patients with non-SVR (p<0.001). Moreover, SVR was related to a reduced risk of HCC development (p=0.017).

The elimination of HCV by IFN-free direct acting antiviral (DAA) therapy is believed to suppress hepatic carcinogenesis, and its use in patients with HCC to prevent recurrence after curative treatment is acceptable. However, a controversial Spanish study published in 2016 raised concerns that IFN-free DAA therapy may promote the progression of HCC. Since this report, many studies have investigated the influence of IFN-free DAA therapy on HCC progression. Several systematic reviews and meta-analyses have shown that IFN-free DAA therapy does not affect HCC recurrence. In contrast, single-center studies have shown that IFN-free DAA therapy may have either promotive or suppressive effects on HCC recurrence.

In an United States study, 20,183 adult HCV patients were exposed to DAAs. For comparison, the authors identified contemporary adult HCV patients without evidence of HCV treatment (n=137.502), and historical HCV patients treated with interferon prior to the introduction of DAAs (n=12,948). Relative to untreated HCV patients, DAA-treated patients were older, more likely to be male, and more likely to have cirrhosis at baseline. After adjustment, DAA treatment was associated with a significantly reduced risk of liver cancer relative to no treatment (adjusted HR=0.84, 95% CI: 0.73-0.96), and relative to interferon-based treatment in the pre-DAA era (HR=0.69, 95% CI: 0.59 – 0.81).

In this talk, the summary of IFN-based and IFN-free DAA therapy in terms of association with HCC risk will be presented.



Non-Viral Managements to Prevent HCC

Dong Hyun Sinn

Sungkyunkwan Univ., Korea

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide, with growing incidence and mortality in both Western and Asian countries.[1,2] HCC typically occurs in patients with chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection.[3,4] The use of antiviral agents, such as nucleos(t)ide analogs (NAs) or direct-acting antivirals (DAAs), has significantly decreased the HCC risk; however, it does not completely eliminate the risk of HCC, including those with advanced fibrosis.[5] Therefore, effective strategies focused on preventing the development of HCC in at-risk population remains a clinical unmet need. Herein, we will discuss several possible ways to decrease development of HCC by non-viral management.

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Risk-Stratified Surveillance for Hepatitis Virus-Associated HCC

Shuichiro Shiina

Juntendo Univ., Japan

In order to demonstrate the effectiveness of surveillance, it must be shown that early detection increases the chances of receiving curative treatment and contributes to the improvement of prognosis. HCC is a cancer that is easy to define high-risk groups, and under this method, surveillance has been widely conducted for high-risk groups, mainly patients with hepatitis virus-related chronic liver diseases. On the other hand, high-risk groups of developing HCC are high-risk groups for recurrence after curative treatment. There is a problem that early detection and early treatment do not necessarily lead to a cure for the disease.

High-risk groups for developing HCC are patients with cirrhosis, chronic hepatitis B, and hepatitis C. Extremely high-risk groups are those with cirrhosis type B and C. Furthermore, those who undergo treatment for HCC should be considered in an ultra-high- risk group. Even in those who undergo a curative treatment, 70 -80 % develop recurrence within 5 years. Although the rate of developing HCC decreases in patients with chronic hepatitis B who are taking nucleic acid analog agents and those with chronic hepatitis C who have achieved SVR, there is still a considerable risk, so surveillance must be continued.

High-risk groups should be screened every 6 months and extremely high-risk groups every 3-4 months using the US and tumor marker measurements, such as AFP, DCP, and AFP-L3. In patients with liver atrophy, severe obesity, and post-operative deformity in whom the whole liver cannot be scanned by the US, dynamic CT/MRI should be used. When the US detects new nodules, dynamic CT/MRI should be carried out for differential diagnosis. Even when no tumor is detected by the US, dynamic CT/MRI should be considered in those with persistent elevation of tumor markers. In contrast-enhanced imaging, "typical imaging findings of HCC," is intense arterial enhancement followed by washout of contrast materials in the venous delayed phases.

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Symposium 2-8. AI and Machine Learning for Liver Disease Management

Chairs:

Il Han Song (Dankook Univ., Korea)

Moon Seok Choi (Sungkyunkwan Univ., Korea)

Developing AI Model for Predicting HCC

Hwi Young Kim

Ewha Womans Univ., Korea

Hepatocellular carcinoma (HCC) is a serious global health threat and the second-most common cause of cancer-related mortality worldwide.[1] Chronic hepatitis B (CHB) remains one of the leading causes of HCC despite vaccination and effective treatment, especially in East Asia.[2] The overall risk of HCC in patients with CHB is estimated to be between 10 and 25% during their lifetime.[3] Evidences suggest that the risk of HCC occurrence can be lowered, albeit incompletely, by antiviral treatment, primarily with nucleos(t)ide analogues (NAs).[4-7]

Current practice guidelines recommend surveillance for early HCC detection and potentially curative treatment in patients with CHB, with specifying higher-risk subgroups in some guidelines.[8-10] Ideal programs for surveillance should take into account individualized risk of HCC in potential candidates. However, CHB patient population encompasses heterogeneous subgroups with diverse levels of risk at any given time point.[11] In the current era of potent NA treatment, more accurate prediction of HCC risk would be anticipated with individualized risk stratification. In addition, more comprehensive approaches to develop novel prediction models including artificial intelligence (AI)-assisted methods and independent validation of such models are under investigation.

In this regard, various risk scores have been developed to predict HCC occurrence in patients with CHB treated with or without NAs during the last couple of decades.[12-20] These risk scores are mostly based on various combinations of risk variables, such as disease-related factors (e.g., serum HBV DNA level, HBeAg status, presence of fibrosis) and host factors (e.g., age, sex, comorbidities), which exhibit acceptable performances with the reported areas under the receiver operating characteristic curve between 0.6 and 0.8.[21-26] NA therapy should also be considered for risk stratification, which may modify some of the abovementioned HCC risk factors. We recently developed an AI-based HCC risk prediction model for patients with CHB receiving a potent NA treatment from large-scale Korean and Caucasian cohort datasets using a gradient-boosting machine (GBM) algorithm ("Prediction of Liver cancer using Artificial intelligence-driven model for Network - hepatitis B (PLAN-B)" model; https://www.planbhcc.com).[27] This PLAN-B model consists of 10 baseline parameters including the presence of cirrhosis, age, platelet count, antiviral agent, sex, serum ALT, serum HBV DNA, albumin, bilirubin levels, and HBeAg status. This model showed satisfactory discriminant function (c-index, 0.82), which was significantly better than other models for both the Korean (PAGE-B, modified PAGE-B, REACH-B, and CU-HCC) and Caucasian validation cohorts (PAGE-B, REACH-B, and CU-HCC). The calibration function was also satisfactory for each cohort. Moreover, this model aided in the identification of the minimal-risk group (0.0% HCC risk up to 5 years of follow-up), which may help individualize surveillance programs for affected patients. Further studies are warranted for development of AI prediction models in other at-risk populations for HCC, including metabolic

dysfunction-associated steatotic liver diseases.

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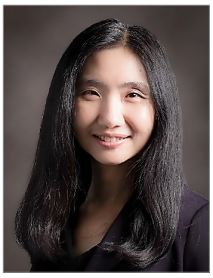

Radiomics and Deep Learning for Chronic Liver Disease

Roongruedee Chaiteerakij

Chulalongkorn Univ., Thailand

Radiomics is a rapid evolving field of medical image analysis that involves extracting a large number of features from various radiological imaging modalities, particularly computed tomography and magnetic resonance imaging. These radiomic features are unique to each individual patient, as they capture heterogeneous disease characteristics and patterns imperceptible to the human eye. In the context of chronic liver disease, radiomics has been extensively studied for its application in diagnosing, predicting treatment responses, determining prognosis, and guiding treatment plans for hepatocellular carcinoma. Its utility has also been explored for the assessment and staging of liver steatosis and fibrosis.

There are 2 key stages in developing radiomics models. The first stage is to extract a wide range of prespecified features from the images, such as size, shape, texture, signal intensity, and other relevant lesion attributes. The feature extraction is performed using advanced mathematical algorithms to "quantify" the characteristics of the region of interest in the image. This quantitative information provides the basis for the following stage, which involves the use of deep learning algorithms to develop predictive models for diagnosis and prediction of patient outcomes, resulting in precision-guided therapeutic approaches. This enhanced capability is attributed to deep learning algorithms' inherent ability to distinguish intricate patterns and relationships within massive and complex datasets.

Currently, there are several challenges in integrating radiomics into clinical practice, including a lack of standardized process for the feature extraction phase, the high dimensionality of radiomic data, and the requirement for large volumes of high-quality data to develop effective radiomic models. Most models were developed using dataset from single centers and have not been undergone external validation. Despite these challenges, radiomics has shown great promise as a non-invasive tool in improving both diagnosis and prognosis, and also offering potential in guiding personalized therapy for chronic liver disease.

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Harnessing Knowledge and Experimental Data Using AI Drug Discovery Technology

Hanjo Kim

Standigm, Korea

The realm of 'AI Drug Discovery' converges two significant domains: Artificial Intelligence and Drug Discovery, encompassing a broad spectrum of related concepts and applications. Numerous scientists operating in the pharmaceutical sphere have identified AI technology as an advanced tool instrumental in disciplines such as chemistry and biology. As these professionals seek innovative tools to augment productivity, any corroborated method can vie for this objective. AI-driven approaches have begun to demonstrate their dominance across a multitude of applications. Several organizations are experimenting with AI algorithms to revolutionize decision-making processes in drug discovery and development, particularly harnessing data-driven decisions that exploit the vast data reservoirs available.

Considering the adoption of AI-facilitated tools in drug discovery, numerous pivotal occurrences have emerged, including AlphaGo, clinical-stage compounds designed by AI[1], AlphaFold2[2], generative AI models like ChatGPT[3], and the scientific community's reaction to these developments[4].

Employing knowledge graph database technology[5] is a significant methodology for efficacious analysis of the extensive biological data available. It helps uncover hidden associations between various biological entities and prioritize relevant ones in contexts related to the pharmaceutical industry. This process balances two distinct strategies: a bottom-up approach that ensures the scientific accuracy of individual research conducted in specific contexts and a top-down approach that links different levels of research-generated knowledge to comprehend connection meanings. This can be characterized as the amalgamation of molecular biology and systems biology. In this context, Standigm ASK™[6], a target prioritization platform technology developed by Standigm, is noteworthy.

From a drug discovery perspective, the most intricate and time-consuming process involves crafting novel molecular structures that fulfill two primary criteria: synthetic feasibility and patentability. The emergence of generative chemistry models[7] has catalyzed the automation of the design-make-test-analysis (DMTA) cycle by facilitating the generation of novel molecular structures with desired attributes such as biological activities, ADME/Tox properties, synthetic simplicity, and patentability. Given an appropriate scientific representation, this capability can be extended to any modality, encompassing small molecules, proteins, and antibodies.

It is widely acknowledged that the performance of AI models is contingent upon the volume and quality of data. Given that drug discovery projects involving novel biology and chemistry may not provide sufficient data for AI models, procuring adequate data presents one of the largest challenges in AI drug discovery. Potential solutions to this issue may include automating experiments to curtail data costs or implementing few-shot learning algorithms that learn broader scientific concepts and leverage minimal

data to generate fine-tuned models.

Incorporating AI technology into drug discovery and development projects inherently implies reimagining entire workflows to optimize productivity enhancement, thereby potentially catalyzing a fundamental transformation of pharmaceutical R&D itself.

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Deep Learning-Based Prediction of Biomarkers Using Liver Cancer Histopathological Images

Sung Hak Lee

The Catholic Univ. of Korea, Korea

The morphological interpretation of histologic sections forms the basis of diagnosis and prognostication for cancer.

There has been an exponential growth in the application of an artificial intelligence (AI) in pathology image analysis. Deep learning (DL), an AI technology, is a representation learning approach ideally suited for image analysis challenges in digital pathology. DL methods for digital pathology analysis are an effective way to address multiple clinical questions, from diagnosis to prediction of treatment outcomes.

Molecular alterations in cancer can cause phenotypic changes in tumor cells and their micro-environment. Advances in DL have enabled the extraction of previously hidden information directly from routine histology images of cancer, providing potentially clinically useful information.

Currently, survival is estimated by clinical parameters such as age, gender, cancer stage, pre-existing conditions, genetic alterations and histology risk factors. In addition to these established risk factors, higher-level features from pathology images carry prognostic information.

We hypothesized that image analysis is a cost-effective tool to associate complex features of tissue organization with molecular and outcome data. Here, we outline emerging concepts of how DL can extract biomarkers directly from liver cancer pathology images and show that DL can consistently infer a wide range of tumor subtypes, genetic mutations, and molecular biomarkers directly from routine histology. We will also demonstrate that the model is more accurate in predicting patient survival than using current pathology practices.

The use of deep learning in pathology imaging has the potential to improve diagnostic accuracy and ultimately improve patient outcomes. The implementation of AI tools can be considered as a paradigm shift that will change pathology fields in the era of precision medicine.

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DAY 2 | Friday, Sept. 22, 2023

SIG 2. cccDNA and HBV Integration: Stumbling Blocks for HBV Cure

Chairs:

Kyun-Hwan Kim (Sungkyunkwan Univ., Korea)
Byung-Cheol Song (Jeju Univ., Korea)

HBV cccDNA: Mechanism of Its Formation and Therapeutic Targets

Kyun-Hwan Kim

Sungkyunkwan Univ., Korea

The current antiviral drugs can efficiently control but not eliminate HBV in the carriers at risk to develop liver diseases and cancer. HBV patients often require lifelong therapies and cure is still a challenging goal because HBV establishes a stable nuclear persistence form, the so-called HBV cccDNA, in infected hepatocytes. Therefore, targeting HBV cccDNA is a critical issue if we want to cure HBV infection.

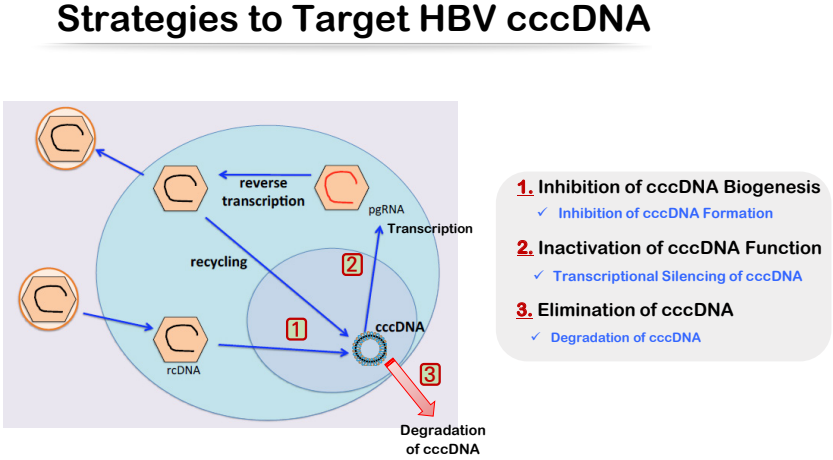
Recently, cellular factors involved in cccDNA formation have been identified. Five core components of DNA lagging-strand synthesis including PCNA, RFC, POLδ, FEN-1, and LIG1 are required for cccDNA formation to repair the plus-strand of rcDNA, but only FEN-1 and LIG1 are required to repair the minus strand.

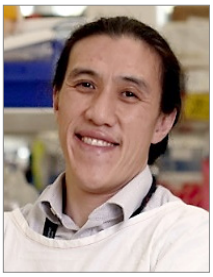
HBV cccDNA can be targeted by several approaches. 1) The cellular factors or enzymes involved in cccDNA formation can be targeted to inhibit cccDNA synthesis. 2) cccDNA can be degraded by treatment with antiviral cytokine. The cellular factors in this process can be targeted to accelerate the degradation of cccDNA. 3) cccDNA can be inactivated by transcriptional silencing or epigenetic modifications.

Since it is currently almost impossible to remove cccDNA from infected hepatocytes, inhibition of cccDNA function through its transcriptional silencing is a realistic goal to achieve functional cure of HBV infection. Combining induction of immune control to safely eliminate infected cells will accelerate the functional cure of HBV infection. These approaches will be introduced in this presentation.

In this talk, I review the recent scientific advances in HBV cccDNA study. Especially, I will focus on the action mechanisms of cccDNA targeting strategies in detail.

Keyword: hepatitis B virus (HBV), covalently closed circular DNA (cccDNA), HBV cure, capsid inhibitor, cccDNA Inhibitor.





HBV Integration and Liver Cancer

Thomas Tu

Westmead Institute for Medical Research, Australia

One of the world's greatest infectious public health concerns is chronic infection with the Hepatitis B virus (HBV) that affects >360 million people. HBV infection increases the risk of liver cancer by 100-fold resulting in a 25-40% lifetime risk of liver-related morality and killing 660,000 people annually. Our group's research is dedicated to reducing the HBV-associated liver cancer burden by understanding how the virus drives cancer and developing clinical risk markers for earlier diagnosis.

A likely driver for HBV-associated cancer is integration of the virus DNA into the cellular DNA. Though only 1 in ~10,000 hepatocytes have integrations, they are present in almost all HBV-associated liver tumours, suggesting that integrations are pro-carcinogenic. Even after a chronic HBV infection is cleared, virus integrations persist, as does liver cancer risk.

All known isolated cell clones containing HBV DNA integrations from natural infections appear to have accumulated multiple mutations and translocations. However, it is unclear what the underlying cause of this genomic instability is: in particular, do integrations simply occur at sites of fragile DNA (passenger) or are they the cause of DNA instability (driver)?

The process of HBV DNA integration

To explore the passenger role, we should understand the mechanisms underlying the integration process. Our group's work has demonstrated that HBV integrations are present not only in tumours, but also *early* in infection. Once established, integrations are incredibly difficult to eliminate from the liver. Recent clinical studies have shown that with long-term suppression of viral replication, the reduction of integrated forms in the liver is around 0.5 log after 3 years. Thus preventing the establishment of integrations is likely the most efficient method to reduce of integration burden.

The factors that drive HBV DNA integration remain relatively unexplored. In Hepg2.2.15 cells (a stable expression cell model of HBV), oxidative stress through H_2O_2 has been shown to increase integration 10-fold, however what factors contribute to integration in vivo is still unknown. Their identification is likely to provide clues on the specific molecular mechanisms involved in the integration process, thereby providing suitable targets to inhibit new integration events and potentially limiting the increasing risk of HCC in chronic HBV patients. These may include HBV DNA levels, relative proportion of HBV relaxed circular vs double-stranded linear forms, or inflammatory events.

The effects of HBV DNA integration

To explore the driver effect, the effects of HBV DNA integration should be studied. Our work has also suggested that the sites of integrations are not responsible for early stages of liver cancer (pre-neoplastic clonal expansion), implying that ongoing cancer risk from HBV infection is instead driven by proteins encoded by integrated HBV DNA.

The HBV X protein (HBx) is known to be drive genomic instability though it is not clear how common transcriptionally active and functional HBx is from integrated HBV DNA. To understand this, our team have developed cell lines that continuously produce reporter viruses, each containing different transgenes (including fluorescent proteins and antibiotic resistance genes). Reporter viruses encoding zeocin-resistance have been used to infect hepatoma cells and selected so that only cells with integrations survive. Thus, we have a unique, simple, high-throughput approach to isolate cells with integrations following a *bona fide* infection and allow us to understand the consequences of this relatively rare phenomenon. To date, we have isolated >100 clones derived from single cells with HBV DNA integrations (1-3 copies per cell). We have shown that clones with integrations appear to have altered response to DNA damage, leading to poorer induction of DNA repair enzymes. Thus it appears that integrations also potentiate DNA damage.

Together, these results start to paint a picture of the formation of liver cancer associated with Hepatitis B. Liver cancer is rarely a "one and done" event; continual destabilising effects are likely needed to progress malignant transformation. A potential mechanism is that HBV DNA integrations induce more fragility within cells and lead to even more integrations, fuelling a feed-forward process and eventually leading to liver cancer. We now have the tools to deeply investigate this hypothesis and can potentially use them to screen for compounds that prevent integrations and its effects.

Genome Editing for cccDNA and Integrated HBV

Jae Young Lee

ToolGen, Korea

Stable maintenance of the hepatitis B viral (HBV) covalently closed circular DNA (cccDNA) has been regarded as the main reason behind persistence of chronic hepatitis B. Furthermore, HBV integration into host genome is found frequently. Although integrated HBV DNA generally not associated with viral replication, it can serve as a source for the hepatitis B surface antigen (HBsAg). Current standard-of-care, a nucleos(t)ide therapies, can reduce virus production and further cellular infection, however, have no influence on cccDNA or expression of viral genes. Therefore, life-long treatment with currently approved anti-HBV therapies is required to prevent rebound. Genome editing technology such as CRISPR/Cas9 showed promises to target cccDNA at least pre-clinically.

Throughout this seminar, I will review attempts to apply genome editing technologies for HBV and discuss promises and potential hurdles that needs to be overcome for clinical translation.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

SIG 3. Immunopathogenesis of Viral Hepatitis

Chairs:

Jeong Heo (Pusan National Univ., Korea)

Eui-Cheol Shin (KAIST, Korea)

Type I and Type III Interferon Responses in Hepatitis Virus Infection

Pil Soo Sung

The Catholic Univ. of Korea, Korea

IFNs are currently classified into three major classes: type I, type II and type III. Among them, type I and III IFNs are considered innate immune response IFNs. IFN-λs (IFN-λ_1 or IL-29; -λ_2 or IL-28A; and -λ_3 or IL-28B) are a new family of IFNs that have been designated as type III IFNs. Since the discovery of IFN-λs in 2003, their functions have been considered to overlap with type I IFNs because signaling via the IFN-λ receptor is similar to that via the IFN-α/β receptor. After binding to their receptors, type I and III IFNs initiate a signaling cascade through the JAK-STAT pathways. The cellular actions are then mediated by the induction of ISGs that have antiviral activity. Early studies of IFN responses in hepatitis virus infection examined the expression profiles of ISGs in the livers of virus-infected chimpanzees. The intrahepatic IFN response is strong and sustained in acute HCV infection, whereas it is weak in acute HAV infection and HBV infection. However, the IFN response is not sufficient for the spontaneous resolution of acute HCV infection.

Our group previously discovered that both HCV and HAV infection causes the induction of IFN-λs. Moreover, we demonstrated that HCV-induced IFN-λs blocks additional IFN-α signaling via U-ISGF3-mediated ISG15/USP18 induction. In this symposium, I summarize the recent data on the type I and III IFN response by different hepatitis viruses.

T-Cell Responses and Immunopathogenesis of Chronic Hepatitis B

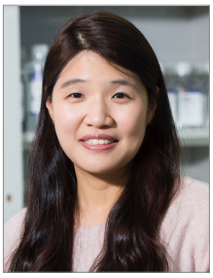
Yuri Cho

National Cancer Center, Korea

Chronic hepatitis B (CHB) remains a significant global health burden, affecting over 250 million individuals worldwide. Despite advancements in antiviral therapies, a considerable number of patients progress to chronicity, leading to the development of severe liver-related complications, including cirrhosis and hepatocellular carcinoma. The immune response plays a pivotal role in determining the outcome of hepatitis B virus (HBV) infection, and T-cell responses, in particular, orchestrate the delicate balance between viral control and immune-mediated tissue damage. Understanding the intricate immunopathogenesis of CHB is paramount for designing targeted therapeutic strategies and enhancing clinical management. The multifaceted interactions between T cells and HBV during chronic infection, lead to the dynamic mechanisms that underlie disease progression.

T-cell responses represent a cornerstone of the immune system's defense against HBV infection. Effector CD8+ cytotoxic T lymphocytes (CTLs) play a central role in recognizing and eliminating HBV-infected hepatocytes. The stimulation of strong, multispecific CTL responses is associated with viral control and disease resolution. However, the persistence of viral antigens, coupled with the functional exhaustion and depletion of antiviral T cells, contributes to viral immune evasion and the establishment of chronicity. Moreover, CD4+ T-helper cells orchestrate immune responses by differentiating into distinct subsets, such as Th1, Th2, and regulatory T cells (Tregs), each exerting varying effects on disease progression. Th1 cells, through the production of interferon-γ, promote antiviral immunity, while Tregs dampen effector T-cell responses, leading to immunotolerance and immunopathogenesis.

The immunopathogenic mechanisms that drive CHB are complex and interconnected, involving a delicate interplay between viral factors and host immune responses. Immune escape mutations in the HBV genome can alter antigen presentation and recognition, thereby evading T-cell surveillance. Furthermore, the liver microenvironment, characterized by a unique immunological milieu, influences T-cell priming and function. The imbalance between pro-inflammatory and anti-inflammatory signals contributes to the suppression of effective T-cell responses and the perpetuation of liver damage. Unraveling the precise interactions between T cells, antigen-presenting cells, cytokines, and chemokines within the liver microenvironment is crucial for deciphering the intricate immunopathogenesis of CHB.



Characteristics of B-Cells in HBV-Associated Chronic Liver Disease

Ji Eun Oh

KAIST, Korea

The liver serves as a vital barrier, separating our internal milieu from the external environment. A unique immune system is established within the liver, capable of swiftly eliminating pathogenic molecules while maintaining tolerance towards harmless antigens. Chronic liver disease (CLD) associated with hepatitis B virus (HBV) spans a spectrum from chronic HBV infection to hepatocellular carcinoma. Although the role of immune cells in the pathogenesis of HBV-associated CLD has been extensively investigated, B cells have received relatively little attention. This presentation aims to provide a concise overview of current knowledge regarding B cells in CLD, shedding light on our ongoing research into the characterization of B cells in CLD patients.

The characteristics of B cells, including B cell subsets and functional attributes, exhibit considerable variability depending on the phase of CLD. In chronic hepatitis B (CHB), an accumulation of $CD21^{-}CD27^{-}$ atypical memory B cells with high expression of inhibitory receptors, such as PD-1, has been observed, resulting in impaired antibody production. In contrast, classical memory B cells predominate in HBV-vaccinated individuals. Intriguingly, HBcAg- and HBsAg-specific B cells in CHB patients exhibit distinct phenotypic and functional differences, underscoring how two components of the same virus can exert varying effects on antiviral B cell function.

Our research involves a comparative analysis of CITE-seq/single-cell RNA-seq (scRNA-seq) data from liver sinusoidal mononuclear cells (LSMC) and peripheral blood mononuclear cells (PBMC) obtained from both healthy donors and patients with HBV-associated CLD. This investigation has unveiled the unique characteristics and distinct composition of B cells in the liver. Notably, the proportion of B cells in LSMC was reduced in CLD patients compared to healthy controls, whereas other cellular populations remained relatively unaffected. Among the B cell subsets, transitional B cells displaying an immature phenotype marked by $CD24^{hi}CD38^{hi}$ and $IgM^{hi}IgD^{hi}$ exhibited the most pronounced decline. As transitional B cells are recognized as regulatory B cells (Breg) in the context of organ transplantation and autoimmune diseases, we postulate that the regulatory function of B cells may be intertwined with the pathogenesis of CLD.

Chronic Hepatitis and Liver Fibrosis in Humans

Hideki Ueno

Kyoto Univ., Japan

Chronic liver diseases cause liver fibrosis. Human hepatic stellate cells (HSCs) play a pivotal role by transitioning from a quiescent state to an activated phenotype, which contributes to the deposition of collagen. Understanding the underlying mechanisms of liver fibrosis and developing effective drugs to combat it require a thorough characterization of HSCs obtained from patients with chronic liver disease. However, there is no established method to isolate, expand, and analyze HSCs from human liver tissue. To our surprise, we recently found that liver perfusate, obtained from healthy donor livers and chronic liver disease patients, contains HSCs. HSCs can be effectively analyzed using flow cytometry, and thus liver perfusate represents a valuable resource for the assessment of HSCs in human liver diseases. The liver perfusate contained both quiescent and activated, but the phenotype of activated HSCs differ between healthy liver and chronically diseased liver. Moreover, we have refined our isolation and expansion protocols for HSCs, enabling us to obtain a reliable and robust supply of these cells. These expanded HSCs have been successfully employed to conduct functional characterizations, shedding new light on their role in liver fibrosis.

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Hepatology Associates - Education Forum 1.
Approach to Various Chronic Liver Disease (*K)

Chairs:

Tae Hun Kim (Ewha Womans Univ., Korea)
Jung Woo Shin (Univ. of Ulsan, Korea)

Treatment of Chronic Hepatitis B: When and Whom?

Jae Yoon Jeong

National Medical Center, Korea

Chronic hepatitis B virus (HBV) infection affected an estimated 296 million individuals globally in 2019, and has a significant public health burden. Chronic hepatitis B (CHB) is a major cause of end stage liver disease such as liver cirrhosis and hepatocellular carcinoma (HCC), which were estimated to cause approximately 820,000 deaths annually. As currently available treatment options cannot eradicate or eliminate HBV, the most realistic goal for HBV treatment is inhibit viral replication, resulting to improve hepatic inflammation, normalize serum ALT level, improve liver fibrosis, reduce the incidence of HCC, and decrease liver-related death. Thus, benefits and risks of antiviral therapy should be carefully evaluated on an individual basis. Antiviral therapy is generally indicated in HBeAg-positive CHB patients with HBV DNA ≥20,000 IU/mL and in HBeAg-negative CHB patients with HBV DNA ≥2,000 IU/mL, serum ALT level is ≥2 times the upper limit of normal, and/or at least significant fibrosis or inflammation on non-invasive tests or liver biopsy while all patients with cirrhosis and detectable HBV DNA should be treated. Patients in the "grey zone" who do not meet the standard criteria for any of the clinical phases (immune-tolerant, immune-active, or inactive phase) should be closely monitored. During follow-up, liver biopsy or non-invasive fibrosis tests can be considered for assessment of the histological lesions to determine whether treatment is needed. Also, antiviral therapy is indicated in patients with HCC to prevent the progression of hepatic dysfunction and reduce HCC recurrence, in patients receiving immunosuppression or chemotherapy to prevent the reactivation of HBV, in HBV-related liver transplantation patients, in patients with co-infections, or in pregnant women with high viral load. In the near future, the treatment indications for CHB will change due to the promising research results and the development of new drugs.

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Diagnosis and Management of Hepatitis C Virus Infection

Woo Sun Rou

Chungnam National Univ.

1. Introduction

Hepatitis C virus (HCV) infection causes chronic hepatitis, which sometimes develops cirrhosis or hepatocellular carcinoma. Chronic hepatitis C accounts for about 15–20% of chronic liver disease in South Korea.[1] The prevalence of HCV infections identified during routine health check-up ranged from 0.60 to 0.78%,[2,3] and the prevalence reported in the 2013–2018 data from the Korea National Health and Nutrition Examination Survey was 0.86%.[4] Patients with chronic HCV may have disease progression even while having normal results on liver function tests. Introduced in the mid-2010s, direct-acting antivirals (DAAs) have led to a significant breakthrough in the treatment of HCV with a sustained virologic response (SVR), defined by undetectable HCV RNA in 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment, of more than 95% even after a short treatment duration.[5-7] Hence, all patients with HCV infection, who are willing to be treated and who have no contraindications for treatment, are eligible for antiviral treatment.[8,9] However, many individuals either remain unaware of their HCV infection or were previously diagnosed but never received treatment. It is crucial to boost treatment rates by actively identifying and treating these hidden patients in addition to preventing the transmission of infection. Therefore, EASL and AASLD/IDSA have recently recommended HCV screening and reflex testing, *i.e.* testing for HCV RNA in the sample obtained for anti-HCV antibody testing.[8,9] This session will focus on the diagnosis and management of HCV based on KASL, AASLD/IDSA, and EASL recommendations for Hepatitis C.[8-11]

2. Diagnosis

Blood tests for HCV diagnosis include HCV antibody testing and HCV RNA testing. The current HCV antibody testing method, which utilizes a third-generation enzyme immunoassay (EIA), has a diagnostic sensitivity and specificity of 97.2–99.0% and 99.8–100%, respectively.[12-14] A positive HCV-antibody test indicates current HCV infection (acute or chronic), a past resolved infection, or rarely a false-positive result. To confirm current HCV infection, HCV RNA testing is used. Persons who have a positive HCV antibody test and undetected HCV RNA test mean that they do not have evidence of current HCV infection. Although additional testing is typically unnecessary, if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen, HCV RNA testing should be retested. False negativity for HCV antibody may be obtained for patients with acute HCV infection, patients on dialysis, and immunocompromised patients. Therefore, among persons with a negative HCV antibody test who were exposed to HCV within the prior 6 months, HCV RNA testing or follow-up HCV antibody testing 6 months or longer after exposure is recommended. HCV RNA testing can also be considered for immunocompromised persons. Currently in clinical practice, HCV antibody testing is used as

a screening test or first line diagnostic test, and HCV RNA testing is used as a definitive diagnostic test.

3. Management

Effective prevention of HCV infection can occur through the use of a vaccine, but vaccine trials are still in early phases or progressing slowly. Therefore, the current approach to prevent HCV infection is to reduce transmission by reducing the exposure to the virus. In addition to a universal prevention strategy to reduce transmission by blood transfusion and unsafe medical procedures including unsafe injection, unsafe dental management, hemodialysis, acupuncture, and other medical devices, specific risk populations should be identified to develop population-specific prevention strategies, such as for people who inject drugs using contaminated injection equipment, people with skin or mucous membrane inoculation, or with exposure of broken skin to contaminated blood. Sexual transmission also occurs especially in the HIV co-infected population, but is at low or no risk in heterosexual couples.[15] Other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease and therapeutic choices, should be systematically investigated. All patients should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies, anti-HIV antibodies and anti-HAV IgG antibodies. HBV and HAV vaccination is recommended for all susceptible persons with HCV infection. Patients who are not immune should be offered HBV and HAV vaccinations. Alcohol consumption and substance abuse should be assessed and quantified, and counseling given. Patients with fatty liver must also engage in exercise and weight loss regimens The presence of diabetes mellitus, obesity and the possibility of drug induced hepatotoxicity are required. When using DAA treatment, it should be emphasized that medication adherence is important for achieving SVR.

1) Pre-treatment assessment

As HCV treatment shifted from pegylated interferon and ribavirin to DAAs, the prediction of treatment responses has been somewhat simplified. However, given that each agent features distinct characteristics, the specific agent and the treatment duration must be chosen in consideration of both the patient's individual characteristics and the specific properties of the drugs. Determining the type and duration of a drug involves a multitude of factors, including the presence of liver cirrhosis, the HCV genotype, the severity of liver disease, prior treatment history, renal function, and drug-drug interaction with concomitantly used drugs.

Before initiating treatment, liver cirrhosis and the severity of liver disease can be assessed based on clinical findings, blood test, imaging studies, liver biopsy, or non-invasive liver fibrosis tests. DAAs interact with a variety of drugs; therefore, its interactions with a patient's current drugs must be reviewed, using tools such as that available on http://www.hep-druginteractions.org. With the recent introduction of the pangenotypic regimen, HCV genotyping is no longer required prior to treatment initiation for all individuals. However, in those with evidence of cirrhosis and/or past unsuccessful HCV treatment, treatment regimens may differ by genotype and thus pretreatment genotyping is recommended. Therefore, where HCV genotype and subtype determination are available and affordable and would not limit access to care, this information remains useful to optimise the results of HCV treatment. In addition, in South Korea, even if treated with the pangenotypic regimen in patients without cirrhosis, pretreatment HCV genotype testing is required due to health insurance reimbursement policies, and in some cases, it may be useful in distinguishing potential virological failure from reinfection.

2) Monitoring during and after treatment

For patients without liver cirrhosis, blood test monitoring is not essential unless the patient develops adverse reactions or shows poor adherence. However, patients with liver cirrhosis may have an exacerbation of liver functions during treatment in rare cases; therefore, blood tests may be performed routinely to check for

liver injury. When introducing a new drug during DAA treatment, drug-drug interaction must be checked. In the past, early virologic response (EVR) was assessed on week 4 to determine whether to continue treatment, but it has not been recommended in recent years. The non-detection of HCV RNA in blood samples using a sensitive molecular method at 12 weeks or 24 weeks after treatment completion is defined as SVR (virologic cure), and both SVR12 and SVR24 are considered endpoints of therapy, with a 99% agreement rate between the two parameters.[16] Patients with pre-existing advanced fibrosis or cirrhosis require HCC surveillance and management of complications of liver cirrhosis. Even after achieving SVR, patients must be educated about the infection pathways and prevention tips to lower their risk of re-infections. If at risk for HCV reinfection, counsel on risk reduction and test for HCV RNA annually or with abnormal liver biochemical test.

3) DAAs

DAAs are antiviral agents that act directly on the lifecycle of HCV and are classified as follows depending on their targets: HCV nonstructural protein (NS) 3/4A protease inhibitors (PI), NS5A inhibitors, and NS5B polymerase inhibitors. NS3/4A PIs are drugs ending in –previr, such as asunaprevir, paritaprevir, grazoprevir, glecaprevir, and voxilaprevir; these block multi-protein cleavage essential for HCV replication. NS5A inhibitors end in –asvir, such as daclatasvir, ledipasvir, ombitasvir, elbasvir, velpatasvir, and pibrentasvir; they inhibit HCV replication and assembly. NS5B polymerase inhibitors end in –buvir, such as sofosbuvir and dasabuvir. DAAs are generally used in combinations. Daclatasvir+asunaprevir was first approved in Korea in April 2015 as an interferon-free DAA regimen, and sofosbuvir+rivabirin, ledipasvir/sofosbuvir, sofosbuvir+daclatasvir, elbasvir/grazoprevir, and ombitasvir/paritaprevir/ritonavir plus dasabuvir were subsequently approved. In January 2018, glecaprevir/pibrentasvir was first approved as a pangenotype regimen, followed by approvals of sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir in February and March 2022, respectively. The recently developed pangenotypic DAAs were widely used, and the licenses for ombitasvir/paritaprevir/ritonavir plus dasabuvir and daclatasvir+asunaprevir were withdrawn in Korea in November 2020 and March 2021, respectively.

4) Treatment

In 2019, the AASLD/IDSA and 2020 EASL guidelines also recommended a simplified HCV treatment algorithm applicable for all genotypes using pangenotypic DAAs. This simplified algorithm targets adults aged 18 years and over without prior HCV treatment history, without liver cirrhosis, or with compensated liver cirrhosis (Child-Pugh A). These individuals can be treated with an 8-week glecaprevir/pibrentasvir regimen or 12-week sofosbuvir/velpatasvir regimen. This simplified treatment algorithm of HCV can increase access to treatment by simplifying the diagnosis and treatment of hepatitis C. However, for patients with genotype 3 and compensated liver cirrhosis, RASs should be evaluated; these patients are not eligible for simplified HCV treatment if they have RAS for Y93H. In addition, the patients with current or a history of decompensated liver cirrhosis, end-stage renal disease, being HIV- or HBs Ag-positive, pregnancy, hepatocellular carcinoma, and liver transplantation also do not qualify for a simplified treatment algorithm. AASLD/IDSA recently updated recommendations for Hepatitis C Guidance. Major changes in this HCV guidance update include new recommendations that address the management of incomplete treatment adherence; updated recommendations regarding simplified treatment with minimal monitoring and expand eligibility; newly expanded treatment and retreatment recommendations for children and adolescents; and management, and treatment recommendations for unique and key populations.[8] Treatment recommendations for HCV infected patients, including treatment- naïve and treatment-experienced patients summarized in Table 1-2 (Hepatitis C Guidance 2023 Update by AASLD/IDSA)[8] and Table 3-4 (Korean insurance coverage criteria).

Table 1. Recommendations for initial treatment of hepatitis C virus infected adults[8]

Regimen	Genotype	Classification	Duration	Rating	Caveats and Other Considerations
Treatment-naive without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir	1–6	Recommended	8wk	I,A[a]	
Sofosbuvir/velpatasvir	1–6	Recommended	12wk	I,A[b]	For genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen.
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12wk	I,A[c]	Not recommended for genotype 6e infection if subtype is known.
	1 without cirrhosis	Recommended	8wk	I,B	Applicable to patients without cirrhosis who are not living with human immunodeficiency virus and whose HCV RNA is <6 million IU/mL.
Elbasvir/grazoprevir	1b, 4	Recommended	12wk	I,A[d]	
	1a	Alternative	12wk	I,A	For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (ie, substitutions at amino acid positions (28, 30, 31, or 93), another recommended regimen should be used.
Sofosbuvir/velpatasvir + weight-based ribavirin	3	Alternative	12wk	IIa,A	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
Sofosbuvir/velpatasvir/ voxilaprevir		Alternative	12wk	IIa,B	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
Treatment-naive with decompensated cirrhosis					
Sofosbuvir/velpatasvir + weight-based ribavirin	1–6	Recommended	12wk	I,A[e]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Sofosbuvir/velpatasvir	1–6	Recommended	24wk	I,A[e]	Applicable to patients who are ribavirin ineligible.
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	12wk	I,A[f]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	24wk	I,A[f]	Applicable to patients who are ribavirin ineligible.

Recommendations are listed by recommended vs alternative and by genotypic activity, evidence level, and alphabetically.
Abbreviations: CTP, Child–Turcotte–Pugh score; HCV, hepatitis C virus; NS5A, hepatitis C virus nonstructural protein 5A; RAS, resistance-associated substitution.
[a]The level of evidence rating is I, B for persons with compensated cirrhosis.
[b]The level of evidence rating is I, B for persons with genotype 5 or 6 infection.
[c]The level of evidence rating is IIa, B for persons with genotype 5 or 6 infection and those with genotype 4 infection and compensated cirrhosis.
[d]The level of evidence rating is IIa, B for persons with genotype 4 infection and compensated cirrhosis.
[e]Only available data for genotype 6 infection are in persons with compensated cirrhosis.
[f]Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

Table 2. Recommendations for retreatment of hepatitis C virus infected adults by prior exposure[8]

Regimen	Geno-type	Classification	Durat-ion	Rat-ing	Caveats and Other Considerations
Sofosbuvir-based treatment failure without cirrhosis or with compensated cirrhosis					
Sofosbuvir/velpatasvir/voxilaprevir	1–6	Recommended	12wk	I,A	For genotype 3 infection with compensated cirrhosis, add weight-based ribavirin if there are no contraindications.
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Alternative	16wk	I,A	Not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4A protease inhibitor regimen (eg, elbasvir/grazoprevir).
Glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir+ sofosbuvir + weight-based ribavirin	1–6	Recommended	16wk	IIa,B	
Sofosbuvir/velpatasvir/voxilaprevir	1–6	Recommended	12wk	IIa,B	For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended (rating IIa, C).
Sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir + glecaprevir/pibrentasvir treatment failure without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir+ sofosbuvir + weight-based ribavirin	1–6	Recommended	16wk	IIa,B	Extension to 24 wk should be considered in extremely difficult cases (eg, genotype 3 infection with compensated cirrhosis) or failure following sofosbuvir + glecaprevir/pibrentasvir therapy.
Sofosbuvir/velpatasvir/voxilaprevir + weight-based ribavirin	1–6	Recommended	24wk	IIa,B	
Sofosbuvir- or NS5A inhibitor–based treatment failure with decompensated cirrhosis					
Sofosbuvir/velpatasvir + weight-based ribavirin	1–6	Recommended	24wk	II,C[a]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	24wk	II,C[b]	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.

Recommendations are listed by recommended vs alternative and by genotypic activity, evidence level, and alphabetically.
Abbreviations: CTP, Child–Turcotte–Pugh score; NS3/4A, hepatitis C virus nonstructural protein 3–4A; NS5A, hepatitis C virus non-structural protein 5A.
[a]Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.
[b]Only available data for genotype 6 infection are in persons with compensated cirrhosis.

Table 3. HCV treatment for treatment-naïve adults with or without compensated cirrhosis according to insurance coverage criteria in South Korea

	DAA regimen	HCV genotype						
		1a	1b	2	3	4	5	6
Without LC	Glecaprevir/pibrentasvir	8 wk						
	Sofosbuvir/velpatasvir	12 wk						
	Sofosbuvir/ledipasvir	12 wk	8#/12 wk	12 wk		12 wk		
	Sofosbuvir + R			12 wk	24 wk	24 wk		
	Elbasvir/grazoprevir	12 wk*				12 wk		
Compensated LC	Glecaprevir/pibrentasvir	8 wk						
	Sofosbuvir/velpatasvir	12 wk**						
	Sofosbuvir/ledipasvir	12 wk				12 wk		
	Sofosbuvir + R			16 wk		24 wk		
	Elbasvir/grazoprevir	12 wk*				12 wk		
Decompensated LC	Sofosbuvir/velpatasvir + R	12 wk						
	Sofosbuvir/ledipasvir + R	12 wk						
	Sofosbuvir + R			16 wk				

*genotype 1a and **genotype 3: RAS testing was required
In case with HIV-uninfected and HCV RNA level <6 million IU/mL
Abbreviations: LC, liver cirrhosis; DAA, direct acting antiviral; HCV, hepatitis C virus; R, ribavirin; wk, weeks.

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Table 4. HCV retreatment in treatment experienced adults with or without compensated cirrhosis according to insurance coverage criteria in South Korea

Previous treatment	DAA regimen	LC	HCV genotype					
			1	2	3	4	5	6
Interferon, PegIFN, Ribavirin	Glecaprevir/pibrentasvir	-	8 wk		16 wk	8 wk		
		+	12 wk		16 wk	12 wk		
	Sofosbuvir/velpatasvir	-	12 wk					
		+	12 wk**					
	Sofosbuvir/ledipasvir	-	12 wk/ 12 wk (+R)	12 wk		12 wk		
		+	24 wk/ 12 wk (+R)	12 wk		12 wk		
	Sofosbuvir + R	-		12 wk	24 wk			
		+		16 wk				
	Elbasvir/grazoprevir	-	12 wk*			16 wk (+R)		
		+	12 wk*			16 wk (+R)		
Simeprevir (or boceprevir or telaprevir) + pegIFN + R	Glecaprevir/pibrentasvir	-	12 wk					
		+	12 wk					
	Sofosbuvir/ledipasvir	-	12 wk/12 wk (+R)	12 wk		12 wk		
		+	24 wk/12 wk (+R)	12 wk		12 wk		
	Elbasvir/grazoprevir	-	12 wk (+R)					
		+	12 wk (+R)					
NS5B (Sofosbuvir)	Glecaprevir/pibrentasvir	-	8 wk		16 wk	8 wk		
		+	12 wk		16 wk	12 wk		
	Sofosbuvir/velpatasvir/ voxilaprevir	-	only 1a, 12 wk		12 wk			
		+	only 1a, 12 wk		12 wk			
NS5A - PI	Glecaprevir/pibrentasvir	-	16 wk					
		+	16 wk					
	Sofosbuvir/velpatasvir/ voxilaprevir	-	12 wk					
		+	12 wk					
NS5A + PI	Sofosbuvir/velpatasvir/ voxilaprevir	-	12 wk					
		+	12 wk					

*genotype 1a and **genotype 3: RAS testing was required
Abbreviations: LC, liver cirrhosis; DAA, direct acting antiviral; HCV, hepatitis C virus; R, ribavirin; wk, weeks.

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Diagnosis and Management of Autoimmune Hepatitis

Young Chang

Soonchunhyang Univ., Korea

Autoimmune hepatitis (AIH) is a chronic liver disease in which the body's immune system mistakenly attacks liver cells, leading to inflammation and potential liver damage. It can range from mild to severe and may progress over time if not properly managed. AIH usually develops insidiously; however, the spectrum of symptoms and clinical manifestations are broad, ranging from asymptomatic to acute hepatitis, and AIH may also develop as fulminant hepatitis. In addition, liver fibrosis has already progressed at the time of AIH diagnosis, and cirrhosis may be already present, or it may even appear as an acute exacerbation of cirrhosis. Therefore, AIH should be considered as a differential disease in most liver diseases regardless of the degree of activity or fibrosis.

Typical AIH presents as a form of chronic hepatitis with autoantibodies, hypergammaglobulinemia, and interface hepatitis in liver biopsy. Nonspecific fatigue is the most common. Loss of appetite, weight loss, muscle aches, joint pain, jaundice, and amenorrhea may be present, but low-grade fever and rash are less common. The diagnosis of AIH is based on the characteristic clinical and laboratory findings (elevated serum aspartate aminotransferase [AST], alanine aminotransferase [ALT] and increased IgG concentration), the presence of characteristic autoantibodies, and compatible histological abnormalities. AIH lacks a signature diagnostic marker, and the diagnosis requires the exclusion of other diseases (viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, drug induced liver disease, Wilson's disease, hereditary hemochromatosis, etc).

The goals of AIH treatment are to minimize the risk of complications caused by drugs, control the liver inflammation, and achieve remission to suppress the progression of liver disease. To achieve these aims, long-term or permanent maintenance therapy after remission is required in most patients with AIH. Prednisolone plus azathioprine (AZA) or prednisolone alone is recommended as the first-line treatment for AIH. After achieving a complete biochemical response in patients with AIH, AZA alone or prednisolone at the lowest dose capable of maintaining remission plus AZA is recommended as the maintenance treatment. Treatment withdrawal is considered in patients with AIH showing complete biochemical remission for at least 2 years. Relapse after treatment withdrawal requires prompt reinstitution of the initial induction therapy in patients with AIH. After achievement of complete biochemical response, transition to a long-term maintenance therapy may be considered.

Surveillance and Diagnosis of HCC

Han Ah Lee

Ewha Womans Univ., Korea

Hepatocellular carcinoma (HCC) surveillance is essential for individuals at risk, primarily those with chronic HBV infection or cirrhosis from any cause. The focus should be on those eligible for curative treatments that can enhance survival. Severity of underlying liver disease and comorbid conditions are crucial factors, while patient demographics like age, sex, race, or ethnicity have shown little impact on surveillance benefits.

Surveillance significantly improves survival in patients with Child-Turcotte-Pugh A or B cirrhosis but offers little benefit in most Child-Turcotte-Pugh C cirrhosis cases, except for those on the liver transplant list, where early-stage HCC can alter transplant priority. Surveillance is not recommended for patients with life-limiting comorbid conditions that cannot be addressed by transplantation or other therapies.

For patients with HCV cirrhosis post-sustained virologic response without cirrhosis, routine HCC surveillance is not recommended, as their risk is significantly lower. Patients with noncirrhotic NAFLD also have low annual HCC incidence, making surveillance not cost-effective. However, advanced fibrosis patients in both groups may benefit from individualized surveillance.

Surveillance is typically done using abdominal ultrasound and alpha-fetoprotein (AFP) every six months. While some alternative imaging modalities like contrast-enhanced MRI have shown promise, they are not routinely recommended, and further validation is needed. Overall, the benefits of HCC surveillance appear to outweigh potential harms, with a focus on selecting high-risk individuals for effective surveillance programs.

Diagnosing hepatocellular carcinoma (HCC) primarily relies on noninvasive imaging criteria or pathology, with biomarkers like AFP not considered sufficiently accurate for diagnosis. Noninvasive imaging, specifically multiphasic CT or dynamic contrast-enhanced MRI, plays a crucial role in HCC diagnosis, especially in at-risk patients with cirrhosis or chronic HBV infection. Both CT and MRI have high specificity, with MRI demonstrating slightly higher sensitivity. However, the choice between the two depends on site expertise and practical considerations.

The LI-RADS diagnostic algorithm, based on imaging features such as tumor size, arterial phase hyperenhancement, delayed washout, and capsule appearance, is widely endorsed for diagnosing HCC. LI-RADS categorizes liver nodules from LR-1 (benign) to LR-5 (HCC) based on these features. LR-5 lesions have a high probability (95%-99%) of being HCC, while LR-4 lesions have a 75% probability and should undergo biopsy or close follow-up. LR-3 lesions have a lower probability (around 30%) and should continue surveillance. LR-M and LR-TIV lesions are suspicious for malignancy, with biopsy recommended in such cases.

For patients without cirrhosis or HBV infection, pathological diagnosis is advised, as LI-RADS criteria are not applicable. Biopsies are also recommended for LR-4

and LR-5 lesions, especially in clinical trials or for molecular analyses, which may inform precision treatment initiatives. Special staining and markers like GPC3, glutamine synthetase, and HSP70 can enhance the accuracy of pathological diagnosis.

While AFP was previously used as a diagnostic criterion, its low sensitivity and specificity have led to its exclusion from HCC diagnosis. Liquid biopsy methods, including circulating tumor DNA-based tests, are under investigation for early detection and diagnosis, but their use is not recommended until validated in larger studies.

In summary, the diagnosis of HCC should be primarily based on noninvasive imaging criteria (LI- RADS) or pathology, with a preference for multiphasic CT or dynamic contrast-enhanced MRI in at- risk patients. Biomarkers like AFP and liquid biopsy methods are not recommended for HCC diagnosis due to insufficient accuracy. The specific management strategy for observed lesions depends on their LI-RADS category, with LR-5 lesions having a high probability of being HCC and LR-4 lesions requiring further evaluation through biopsy or close follow-up.

APASL STC 2023 BUSAN

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Epidemiology, Natural History and Risk Stratification of NAFLD

Yang-Hyun Baek

Dong-A Univ., Korea

Nonalcoholic fatty liver disease (NAFLD) is an increasing cause of liver disease worldwide in parallel with increases in the prevalence of obesity and metabolic comorbid disease. NAFLD is a progressive disease and fibrosis and the presence of steatohepatitis are the primary predictors of disease progression. Most of the screening algorithms proposed to use the non-invasive assessments in a sequential algorithm. Herein, I discuss the epidemiology, natural history of NAFLD and how to evaluate the patients at risk across practice settings.

Epidemiology and Natural history

NAFLD is a leading cause of chronic liver disease worldwide. The prevalence is rising in parallel with increases in the prevalence of obesity and metabolic comorbid disease.[1,2]

Recent meta-analysis estimated that 32% of the adult population is affected by NAFLD although the prevalence of NAFLD varies with the clinical setting, race/ethnicity, and geographic region.[3-8] A meta-analysis by Im et al. reported a similar prevalence of 30.3% in South Korea.[9] A large cross-sectional study of 571,872 Korean males in their early 20s found that even among young adult males, NAFLD prevalence was 13.47%, with an increase from 10.66% in 2015 to 16.44% in 2021 and it showed that the burden of disease is increasing in South Korea.[10]

NAFLD is a progressive disease and it encompasses a spectrum ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), which can progress to liver fibrosis and cirrhosis.[11] Data from meta-analysis and pooled studies demonstrated that fibrosis and the presence of steatohepatitis are the primary predictors of disease progression.[12-14] Systematic review on the prevalence of NAFLD in South Korea reported the prevalence of NASH was 2.2% with different patterns by gender.[9] More recent prospective study showed the prevalence of steatohepatitis is 14% in a large middle-aged US cohort.[15] A study for fibrosis progression is an earlier meta-analysis of cohorts with longitudinal paired biopsies and this data demonstrated that a NAFLD fibrosis progression rate of one stage per 7 years in those with NASH versus 14 years for those with NAFL.[16] Fibrosis progression is affected by many factors such as the presence of comorbid disease, genomic profile, and environmental factors. A recent prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and HCC in patients aged ≥ 50 with type 2 diabetes demonstrated the prevalence of advanced fibrosis and cirrhosis were 14% and 6%.[17] It means that the presence of obesity or diabetes amplified the risk of advanced fibrosis. Many studies have demonstrated the prevalence of NAFLD among patients with T2DM is 2-3 fold higher

than that in the general population or between 60-70%.[18]

The most common causes of death in patients with NAFLD are cardiovascular disease and nonhepatic malignancy, followed by liver disease. NAFLD is an underappreciated and independent risk factor for atherosclerotic cardiovascular disease (ASCVD) even after adjustment for ASCVD risk factor covariates in a large number of investigations.[19-20] The amount of liver fibrosis in patients with NAFLD has been strongly linked to the development of liver-related outcomes and death.[13,21-23] Those with cirrhosis require biannual screening for HCC as well as monitoring for signs or symptoms of decompensation.

Risk stratification of NAFLD

Targeted screening of populations at increased risk for advanced liver disease is advised to identify and manage those with clinically significant fibrosis (stage ≥ 2).[24] Screening in high-risk populations, such as those with T2DM, obesity with metabolic complications, a family history of cirrhosis, or significant alcohol use, may help to identify patients with a significant fibrosis. The prevalence of advanced disease is lower in primary care practices than in hepatology practices. Patients suspected to have NAFLD on the basis of metabolic risk factors or incidentally identified as having fatty liver by imaging should undergo primary risk assessment. The objective of this primary risk

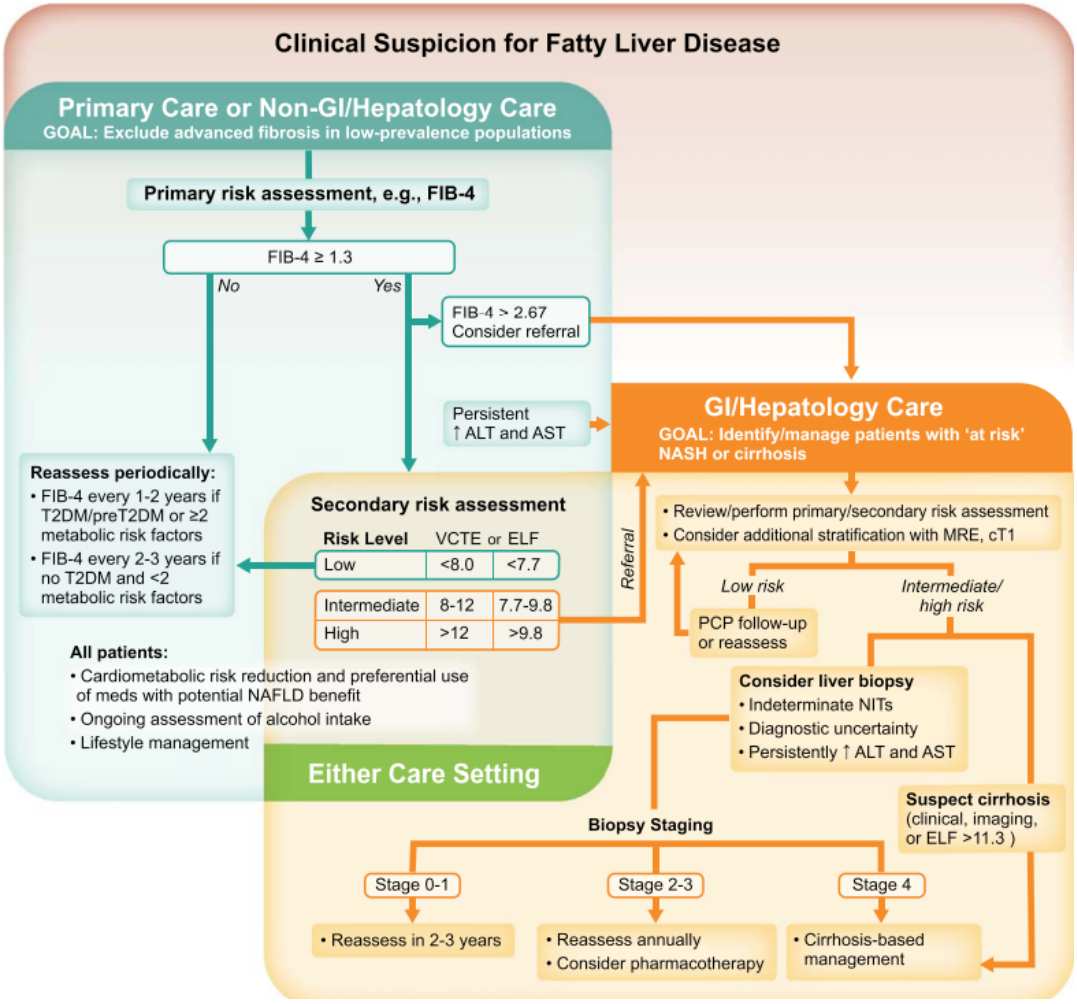

Figure 1. Algorithm for the evaluation of patients at risk for or with established NAFLD across practice settings.[24]

assessment is to identify patients who are not likely to have advanced fibrosis. The most commonly used non-invasive test is the fibrosis-4 index (FIB-4) and this includes four simple parameters; age, platelet, and serum AST and ALT. Patients in low-risk categories based on FIB-4 can be managed in primary care because of the excellent negative predictive value in excluding advanced fibrosis.[25,26] Those who may have a moderate or high risk of advanced disease based on FIB-4 should undergo secondary risk assessment. Vibration-controlled elastography (VCTE) in primary care setting is recommended and the Enhanced Liver Fibrosis (ELF) test could be used if the availability of elastography is limited in some settings.[27] If secondary risk assessment is still consistent with an intermediate or high risk of fibrosis, patients should be referred to specialty care. The primary goal in the specialty care is the identification of patients with "at-risk" NASH or advanced fibrosis. MRI-based tools such as MRE can be used to further risk stratify patients. Liver biopsy should be considered when there is a diagnostic uncertainty or features suggesting an advanced fibrosis. 2023 AASLD practice guidance suggest an algorithm for the evaluation of patients at risk for or with established NAFLD across practice settings. (Fig 1) [23]

Conclusion

NAFLD is a progressive disease and an algorithm based on the non-invasive test is recommended for risk stratification. The goal of the risk assessment is to identify patients who are not likely to have advanced fibrosis in primary care settings and the goal in the specialy care is the identification of patients with "at-risk" NASH or advanced fibrosis. High risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis.

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Lifestyle Intervention and Available Medications in NAFLD Treatment

Se Young Jang

Kyungpook National Univ., Korea

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the accumulation of fat in the liver, which can progress from simple steatosis to non-alcoholic steatohepatitis (NASH) and eventually lead to cirrhosis and liver-related complications. Lifestyle interventions and medications play crucial roles in the treatment and management of NAFLD. This lecture will focus on the management of NAFLD, specifically emphasizing lifestyle changes and the available medications recommended in recent practice guidelines from AASLD and KASL.

Regarding the management of NAFLD through lifestyle changes, strategies include weight reduction, adjustments to dietary habits, engagement in physical activity, and addressing underlying metabolic conditions. Additionally, bariatric surgery is an alternative considered for obese NAFLD management.

Presently, there are no medications approved by the FDA that are specifically designated for treating NAFLD. Nevertheless, there exist medications endorsed for different uses that have demonstrated advantages for NASH through clinical trials. Potential medication options for NAFLD patients encompass Vitamin E, Thiazolidinediones, GLP-1 Receptor Agonists, and SGLT-2 Inhibitors.

It is crucial to emphasize that the selection of treatment, whether it involves lifestyle adjustments, medications, or a blend of both, must be customized according to the unique condition and medical background of each individual. Seeking guidance from a healthcare expert is indispensable to identify the most appropriate strategy for addressing NAFLD effectively.

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Management of Severe Alcoholic Hepatitis

Tae Suk Kim

Kangwon National Univ., Korea

Alcoholic hepatitis (AH) is a syndrome of jaundice and liver failure that occurs in a minority of heavy consumers of alcohol. The diagnosis usually is based on a history of heavy alcohol use, findings from blood tests, and exclusion of other liver diseases by blood and imaging analyses. The management of severe alcoholic hepatitis (SAH) involves a combination of medical interventions, supportive care, and lifestyle changes. SAH is a serious and potentially life-threatening condition that occurs as a result of heavy and prolonged alcohol consumption. It is important to note that immediate medical attention is crucial if someone is experiencing severe alcoholic hepatitis.

Here are some key aspects of the management for severe alcoholic hepatitis:

Alcohol Cessation: The most important step in treating alcoholic hepatitis is to completely stop alcohol consumption. This is essential for preventing further liver damage and allowing the liver to heal.

Hospitalization: Severe alcoholic hepatitis often requires hospitalization for close monitoring and intensive care. Patients with SAH may be critically ill and require medical interventions to manage complications. Since many patients have a long history of excessive alcohol use, they are at risk for alcohol withdrawal. Therefore, the prevention and treatment of alcohol withdrawal is an important part of a patient's management. A systematic review of interventions for alcohol abstinence in patients with chronic liver disease found that when combined with comprehensive medical care, psychosocial interventions such as cognitive behavioral therapy, motivational enhancement therapy, can induce abstinence and reduce the risk of relapse[1].

Nutrition: Malnutrition is common in individuals with severe alcoholic hepatitis. Nutritional support is crucial for healing and improving liver function[2]. Enteral nutrition (feeding through a tube directly into the stomach or small intestine) may be recommended if oral intake is insufficient[3].

Corticosteroids: In addition to general supportive care, we suggest treatment with glucocorticoids (40 mg per day) for patients with severe alcoholic hepatitis (Maddrey discriminant function ≥32) [4,5]. However, the decision to use steroids is based on various factors, including the severity of the condition and the risk of side effects. Not all patients are eligible for steroid treatment, and its effectiveness can vary.

Pentoxifylline: Pentoxifylline is another medication that might be used in certain cases. It has anti-inflammatory properties and can potentially reduce liver inflammation and improve survival in some patients with severe alcoholic hepatitis. However, the use of pentoxifylline in the management of alcoholic hepatitis remains controversial because the data are inconsistent[6-8].

Supportive Care: Patients with SAH may experience complications such as fluid retention, infections, and hepatic encephalopathy (brain dysfunction due to liv-

er failure). Supportive care measures, such as diuretics for fluid management, antibiotics for infections, and medications to manage encephalopathy, are essential.

Liver Transplantation: In some cases, severe alcoholic hepatitis may progress to liver failure despite medical treatment[9,10]. Liver transplantation may be considered as a treatment option for eligible patients who meet specific criteria.

It's important to emphasize that the treatment approach for severe alcoholic hepatitis should be individualized based on the patient's condition, medical history, and overall health. A multidisciplinary team of healthcare professionals, including hepatologists, gastroenterologists, and nutritionists, should be involved in the patient's care to provide comprehensive treatment and support.

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Updated Guideline on Drug-Induced Liver Injury

Nae-Yun Heo

Inje Univ., Korea

Drug-induced liver injury (DILI) is a condition of liver dysfunction caused not only by prescribed medications but also by over-the-counter drugs, herbal and dietary supplements. According to prospective population-based studies, the annual incidence of DILI has been reported as 2.7 to 19 cases per 100,000 persons worldwide.[1] Most cases of DILI recover after discontinuing the causative agent, but in rare instances, they can progress to acute liver failure or chronic liver damage leading to cirrhosis. Therefore, it is crucial to detect the early onset of DILI and manage it properly. However, diagnosing DILI is challenging because it is an exclusion diagnosis, and there is no pathognomonic biomarker for it.

DILI is generally classified into two categories: direct hepatotoxicity and idiosyncratic drug reactions. Direct hepatotoxicity, also known as "intrinsic hepatotoxicity," is a predictable, dose-dependent process that often occurs when a drug is taken in doses exceeding the therapeutic range. Acetaminophen serves as a representative example. Idiosyncratic drug reactions are unpredictable, dose-independent processes that occur in a few patients even when the drug is taken at generally safe levels. These reactions might be due to inheritable or acquired vulnerability to specific drugs. Isoniazid is a well-known example. In some cases, idiosyncratic drug reactions exhibit immune-allergic characteristics (hypersensitivity), such as skin rash, eosinophilia, and lymphadenopathy. A severe form of this reaction is known as DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome.

DILI presents specific clinical phenotypes, including hepatocellular, cholestatic, and mixed patterns, which are characterized by the R value (R=(ALT/UNL)/(ALP/UNL)). The hepatocellular pattern is the most common, with an R value of ≥5, and liver biopsy findings resemble those of viral hepatitis (e.g., Isoniazid, phenytoin, dapsone). The cholestatic pattern ($R \leq 2$) and mixed pattern ($2 < R < 5$) exhibit hepatocyte or canalicular cholestasis on liver biopsy (e.g., anabolic steroid, amoxicillin-clavulanate, phenothiazine). Furthermore, DILI can present with signature patterns such as drug-induced autoimmune hepatitis (e.g., Minocycline, nitrofurantoin, hydralazine), drug-induced steatosis/steatohepatitis (e.g., Tamoxifen), sinusoidal obstruction syndrome (e.g., Busulfan, cyclophosphamide, pyrrolizidine alkaloid), and hepatic adenoma (e.g., oral contraceptives, anabolic hormones, danazol). Recently, immune checkpoint inhibitor-induced DILI has also been reported.[2]

When DILI is suspected, careful assessment of the patient's drug history is essential. Typically, idiosyncratic DILI manifests within 2-24 weeks of starting a new medication, although certain drugs may have longer latency periods (e.g., nitrofurantoin, methotrexate). In contrast, hypersensitivity reactions and direct hepatotoxicity due to acetaminophen can have very short latency periods, often appearing within 24-72 hours. Collecting clinical data after discontinuing the drug (dechallenge) and, in some cases, rechallenging

with the drug is crucial. Physicians can refer to online resources for information on the suspect drug, such as LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/). Furthermore, they should rule out alternative diagnoses, including viral hepatitis (HAV, HBV, HCV, HEV), alcoholic liver disease, nonalcoholic steatohepatitis (NASH), autoimmune hepatitis (AIH), and Wilson disease. Ultrasonography is a common imaging tool for initial diagnosis, and CT or MRCP may be necessary to evaluate bile duct obstruction.[1,2]

Causality assessment is a structured systemic scoring system used to evaluate patients with suspected DILI. It includes the Modified RUCAM score, Maria-Victorino CDS score, and a structured expert opinion process. However, applying these systems strictly in clinical practice can be challenging. The RECAM is a newly developed computerized causality assessment tool that may offer improved reproducibility and reliability compared to RUCAM, but further validation studies are required.[2]

The management of DILI typically involves discontinuing the causative drug and providing supportive care. Specific medical treatments include *N*-acetylcysteine for acetaminophen-induced DILI, cholestyramine for leflunomide-induced DILI, and carnitine for valproic acid-induced DILI. Steroids may be used for drug-induced autoimmune hepatitis (AIH), DRESS syndrome, and DILI resulting from immune checkpoint inhibitors. However, if signs of acute liver failure such as coagulopathy and encephalopathy are present, liver transplantation should be considered. Therapeutic rechallenge with certain drugs, such as those used in tuberculosis treatment or oncology, should be approached cautiously and take into account the risk-benefit assessment of the drug.[2]

Today, many new candidate drugs are withdrawn from clinical trials due to evident hepatotoxicity. Nevertheless, there is still a possibility of detecting idiosyncratic DILI for newly launched medications during post-marketing surveillance. Therefore, it is essential to remain vigilant for adverse effects when physicians prescribe a novel drug to a patient.

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APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Hepatology Associates - Education Forum 3.
Cirrhosis and Complications: Case-Based Learning (*K)

Chairs:

Chang Hyeong Lee (Daegu Catholic Univ. Korea)
Young Seok Kim (Soonchunhyang Univ., Korea)

Diagnosis and Management of Ascites and Related Complications

Chang Hun Lee

Jeonbuk National Univ., Korea

Ascites stands as one of the most prevalent complications associated with liver cirrhosis, often serving as the initial sign of decompensated cirrhosis with portal hypertension.[1] It is estimated that 5% to 10% of patients with compensated cirrhosis develop ascites annually.[2] The emergence of ascites has been consistently associated with a poor prognosis.[3] The pathogenesis of ascites and related complications in cirrhosis is multifaceted. The central event revolves around effective arterial underfilling resulting from splanchnic vasodilation, leading to the activation of vasoconstrictor factors such as renin-angiotensin. Portal hypertension further contributes to increased sinusoidal hydrostatic pressure and heightened gut permeability, allowing bacterial translocation and exacerbating the pathogenesis of complications associated with ascites, such as hyponatremia, spontaneous bacterial peritonitis (SBP), acute kidney injury (AKI), and hepatorenal syndrome (HRS).[4] Herein, we aim to review the diagnosis and management of ascites in the context of liver cirrhosis and its associated complications.

The diagnostic evaluation of ascites should primarily encompass a comprehensive assessment, including a thorough patient history, physical examination, abdominal doppler ultrasound, and laboratory assessment of liver and renal function. Ascitic fluid analysis, including cell count, differential, and biochemical tests, is essential to determine the underlying cause and guide treatment decisions. Ascites due to portal hypertension typically presents with a Serum-Ascites Albumin Gradient of 1.1 or higher and an ascitic fluid protein level below 2.5.[4] The severity of ascites is classified into three grades: Grade 1, which is detected only by imaging techniques; Grade 2, identified by visual inspection and palpation; and Grade 3, profound distension of the abdomen.[1]

The primary therapeutic approach for ascites centers around the management of the underlying liver disease.[5] Potential treatment modalities encompass nutritional support, sodium restriction, and diuretic therapy. Aldosterone antagonists, such as spironolactone, are the primary diuretics used in cirrhotic ascites, and loop diuretics like furosemide can be combined to enhance diuretic effects and maintain normal serum potassium levels.[6] In grade 3 ascites, therapeutic large-volume paracentesis can be considered. Refractory ascites, characterized by diuretic resistance or intractable ascites recurrence after paracentesis, the primary approach involves large-volume paracentesis, with additional consideration for the implementation of Transjugular Intrahepatic Portosystemic Shunt, alongside concurrent preparations for liver transplantation.

In patients with liver cirrhosis, complications related to ascites include SBP, AKI, and HRS. SBP is a complication related to ascites and refers to the occurrence of bacterial infection within the peritoneal cavity which can be diagnosed when the polymorphonuclear leukocyte (PMN) count in ascitic fluid is 250/

mm^3 or higher in the absence of a clear source of infection.[6] Even when the PMN count is below 250/mm^3, empirical antibiotic therapy is recommended if there are symptoms or signs of infection. On the other hand, AKI is a common and poorly controlled complication of cirrhosis. The International Club of Ascites defines AKI as an increase in serum creatinine by 0.3 mg/dL or more within 48 hours or an increase of 50% or more from baseline within one week. For cirrhotic ascites patients with AKI, unresponsive to a 2-day diuretic interruption and plasma expansion (1 g of albumin per kilogram of body weight, up to 100 g), hepatorenal syndrome is diagnosed. Diuretics should be discontinued in cirrhotic patients who develop AKI or hepatorenal syndrome. Terlipressin in combination with albumin is recommended for the treatment of hepatorenal syndrome.[7,8] The ultimate treatment for hepatorenal syndrome is liver transplantation.

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Diagnosis and Management of Acute Variceal Bleeding

Seong Hee Kang

Korea Univ., Korea

Portal hypertension (PH) develops because of increased resistance to portal flow and is enhanced by the presence of increased portal collateral blood flow. Esophageal varices develop because of PH, which is traditionally assessed indirectly by determining the hepatic venous pressure gradient (HVPG): PH is defined as an HVPG >5 mmHg, while clinically significant portal hypertension is defined in presence of a gradient >10 mmHg.[1] Gastroesophageal varices (GEVs) are a frequent complication of liver cirrhosis and a leading cause of mortality in patients with liver cirrhosis. Esophageal varices are the most common type of GEVs, with a prevalence of 50% to 60% among patients with cirrhosis, and up to 85% in patients with decompensated cirrhosis. Gastric varices are present in about 20% of patients with cirrhosis, and they can be of different types.[2] Esophageal varices are classified by size (small, medium, or large) and by the presence of red wale marks,[3] while gastric varices are classified as gastroesophageal varices (GOV) or isolated gastric varices (IGV).[4]

When the portal pressure increases above a threshold, collaterals develop at the site of communication between the portal and systemic circulation, of which GEVs are the most important. With the aggravation of portal hypertension, the collaterals grow and eventually rupture. Acute variceal bleeding is a life-threatening complication of cirrhosis, but the mortality associated with it has decreased with current management based on careful blood transfusion, vasoactive medications, antibiotics, and endoscopic and pre-emptive trans jugular intrahepatic portosystemic shunts. Prevention of recurrent variceal hemorrhage is based on the combination of nonselective beta-blockers and endoscopic variceal ligation.[5]

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When Is the Appropriate Time for Liver Transplantation?

Kwang Il Seo

Kosin Univ., Korea

Liver Cirrhosis

When liver cirrhosis progresses to decompensated status, it is time to consider the liver transplantation. In case of Child-Pugh score C, transplantation is recommended. However, it is essential to consider factors such as mortality due to complications of cirrhosis and the risks associated with transplantation surgery, including immunosuppressive drug use.

Ascites controlled by diuretics does not necessarily require immediate transplantation. The decision should be based on the overall health status of the patient. For patients with refractory ascites, active consideration of transplantation is advisable. Whenever possible, it is best to decide on transplantation before the development of peritonitis.

Patients with esophageal variceal bleeding are not recommended to receive immediate liver transplantation after a single bleeding episode. Clinically, transplantation is considered when repeated variceal bleeding occurs. In cases of gastric variceal bleeding, liver transplantation could be considered earlier than esophageal varix bleeding.

Hepatic encephalopathy does not warrant immediate consideration for transplantation with a 1-year survival rate of approximately 70%. However, repeated occurrences of hepatic encephalopathy should prompt consideration of transplantation.

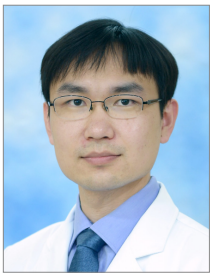
Spontaneous bacterial peritonitis should lead to preparation for transplantation after medical treatment. Patients with recurrent peritonitis remain at high risk for intra-abdominal infections even after transplantation.

Alcoholic cirrhosis can be challenging to differentiate from acute alcoholic hepatitis clinically. When liver function and renal function deteriorate simultaneously, the Model for End-Stage Liver Disease (MELD) score can be very high. Abstinence and conservative treatment can lead to improvement in some cases. Therefore, if a patient's condition is not severely compromised, it may be advisable to wait before proceeding with transplantation.

Hepatocellular Carcinoma

For patients meeting the Milan criteria, liver transplantation is a method to reduce recurrence and increase survival rates. However, even with small tumor sizes, aggressive tumor biology in hepatocellular carcinoma with high AFP and PIVKA levels can increase the risk of recurrence. In patients with tumor markers AFP >1000, transplantation may be considered if stable conditions persist for more than 6 months after downstaging.

For cases beyond the Milan criteria (Over-Milan), proceeding with transplantation after downstaging, if possible, can be beneficial in reducing the risk of recurrence.



Treatment Strategy Based on HCC Stage

Jung Hwan Yu

Inha Univ., Korea

In this lecture, each staging system for HCC and the process of determining treatment methods for actual patients with HCC will be described. Hepatocellular carcinoma (HCC) is the third-leading cause of cancer death worldwide. Despite its enormous global impact, there is much disagreement about how best to stage and characterize this cancer. The differences in approach to HCC are due in part to its inherent clinical and biologic heterogeneity, but are also a function of the prism through which clinicians and clinical researchers observe the cancer. Despite numerous validation and comparative studies, and "consensus" panel recommendations generated by hepatologists, oncologists, surgeons and radiologists, with varying degrees of multidisciplinary collaboration, there is still no single system that could be called the "standard" for classifying HCC.

Like with any cancer, the goals of a tumor staging system in HCC are to estimate a patient's prognosis, which allows for appropriate therapy to be selected. The identification of that appropriate therapy, in turn, requires a staging paradigm that standardizes the platform for researchers to exchange data regarding treatments and outcomes. Ideally, and most challenging with HCC, staging systems should assure balance of important prognostic factors across treatment arms within a clinical trial population to avoid confounding of outcomes by baseline differences.

The new TNM according with the AJCC has only internal validation, and is based on series of patients undergoing resection, as is the case with the seminal paper proposing JIS classification. Pathologic information is needed in all cases, this representing a limitation for wide clinical use. The BCLC staging system has been validated by a surgically oriented European group. This study includes the widest comparison among staging systems, in comparison with other retrospective studies in which the limited collection of data impairs the ability to test all the systems available.

APASL STC 2023 BUSAN

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"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Early Morning Workshop 1. Emerging Risk Factors of HCC in Chronic Hepatitis B

Chair:

Diana A. Payawal (Fatima Medical Univ. Philippines)

Impact of Metabolic Factors on the Risk of HBV-Related HCC

Yun Bin Lee

Seoul National Univ., Korea

Despite the widespread use of vaccines, chronic hepatitis B (CHB) is one of the most common chronic viral infections worldwide, and especially in Asian countries.[1] Although the long-term prognosis for CHB patients has been improved by antiviral therapy with potent nucleos(t)ide analogues (i.e., entecavir, tenofovir disoproxil or tenofovir alafenamide), the risk for developing liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) has not been eliminated in those patients, leading to a huge burden on public health.[2-5]

Nonalcoholic fatty liver disease (NAFLD) is another serious global health problem because of the increasing prevalence even in Asian countries. Although its pathogenesis is not fully understood, NAFLD is primarily associated with obesity and insulin resistance, and is regarded as a hepatic manifestation of metabolic syndrome.[6] A diverse spectrum of liver diseases including nonalcoholic steatohepatitis and liver cirrhosis results from NAFLD, and NAFLD is a well-known risk factor for HCC.[7] Theoretically, NAFLD and chronic hepatitis B virus (HBV) infection may synergistically potentiate HCC development.

We previously reported a study evaluating the effect of histologically proven fatty liver on the development of HCC in CHB patients.[8] In this study, we included 321 consecutive CHB patients without significant alcohol consumption undergoing liver biopsy and subsequent histologic diagnosis and analyzed the association between hepatic steatosis (≥ 5%) and the risk for HCC. Our study demonstrated that the prevalence of histologically proven fatty liver was 21.8% in patients with CHB, and coexisting fatty liver was associated with a 3–fold increased risk for developing HCC (adjusted hazard ratio [HR] 3.005, 95% confidence interval [CI] 1.122–8.051; p=.03). However, after inverse probability weighting based on each patient's propensity score to rigorously adjust for patient characteristics, including metabolic factors, no significant association between coexistence of fatty liver and HCC development was observed (adjusted HR 1.709, 95% CI 0.404–7.228; p=.47). In contrast, diabetes was significantly associated with the risk for developing HCC (adjusted HR 3.562, 95% CI 1.117–11.359; p=.03). These results suggest that superimposed NAFLD as a hepatic manifestation of metabolic syndrome, not hepatic steatosis per se, increases the risk for HCC in CHB patients.

In a previous Taiwanese study, when the influence of metabolic risk factors, such as obesity, diabetes, hypertension, and hypertriglyceridemia, on HCC risk and liver-related mortality in male CHB patients was analyzed, patients with ≥ 3 metabolic risk factors were at a 2.3–fold higher risk for HCC, suggesting a synergistic hepatocarcinogenic effect of metabolic factors and chronic viral hepatitis.[9] We validated an association of the burden of metabolic risk factors with risks of HCC using a large nationwide population-based cohort of CHB patients.[10] In this nationwide population-based study of 317,856 adults with CHB, we demonstrated

that an increasing burden of metabolic risk factors (i.e., obesity, high blood pressure, hypercholesterolemia, and diabetes) was associated with higher risks of developing HCC, non-HCC cancer, and all-cause mortality in a dose-responsive manner (all $P<.0001$ for trend). In another recent nationwide study involving 282,611 non-cirrhotic adults with chronic HBV infection, we confirmed the association between a higher burden of metabolic risk factors and the risk of HBV-related HCC.[11] In addition, our study results suggested the beneficial effect of daily low-dose aspirin therapy for preventing HCC development in patients with a higher metabolic risk factor burden.

On the basis of these study findings, concurrent fatty liver as a hepatic manifestation of metabolic syndrome, may possess important predictive value for HCC rather than hepatic steatosis per se in CHB patients. Thorough assessment and management of metabolic risk factors may be necessary to lower the risk of developing HCC and increase survival in patients with CHB. Moreover, the burden of metabolic risk factors should be considered to establish an individually tailored surveillance strategy for HCC, also in patients undergoing long-term antiviral treatment.

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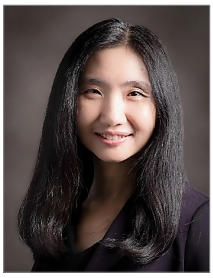

Have Risk Factors for HCC Changed over the Decades?

Roongruedee Chaiteerakij

Chulalongkorn Univ., Thailand

Chronic viral hepatitis B and C infections, along with alcohol consumption, and nonalcoholic steatohepatitis (NASH), stand as established risk factors for liver cancer. Over the past three decades, the distribution of liver cancer causes has undergone significant changes. In 1990, chronic viral hepatitis B infection was the leading cause of liver cancer globally, accounting for 53% of cases. However, by 2019, the burden of hepatitis B-associated liver cancer has dropped to 41%. This decline, notably evident in Asia, can be attributed to HBV vaccination, improved access to treatment, and the availability of potent antiviral drugs. While the proportion of hepatitis B-associated liver cancer decreased, the prevalence of the other three main risk factors increased: hepatitis C infection rose from 23% to 29%, alcohol consumption from 13% to 18%, and NASH from 5% to 7% for NASH during the period from 1990 to 2019.

In recent decades, nonviral factors have emerged as the leading cause of liver cancer-related deaths. NASH has gained prominence as a global risk factor for liver cancer. Between 1990 and 2019, NASH became the fastest-growing cause of liver cancer deaths, followed by alcohol consumption. During this period, the number of NASH-related liver cancer cases and deaths increased by 105% and 95%, respectively. Incidences of NASH-related liver cancer increased with age and were more prevalent among individuals aged over 55 years compared to those aged 20-54 years. Females also had a higher proportion of NASH-related liver cancer than males. Regarding liver cancer attributed to alcohol, the reported annual incidences varied across global regions, ranging from 0.9% to 5.6%. Central Asia, Australasia, and Southeast Asia had the largest number of cases. The burden of alcohol-related liver cancer was more pronounced in males and individuals aged over 40 years. The worldwide number of alcohol-associated liver cancer deaths continued to rise from 1990 to 2019, with the most significant increases occurring in Central Asia and Eastern Europe. Globally, deaths resulting from alcohol-associated liver cancer were predicted to experience a rapid upsurge over the next 25 years. The substantial increase in the burden of liver cancer caused by nonviral factors can be attributed to lifestyle changes, economic growth, and social development. Accordingly, it is imperative to implement further measures to control these nonviral factors urgently to mitigate the incidences of NASH and alcohol-induced liver cancer.

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APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 2 | Friday, Sept. 22, 2023

Early Morning Workshop 2. Real-Life Experiences in HCV Management

Chair:

Ming-Lung Yu (National Sun Yat-sen Univ., Taiwan)

Are Metabolic Derangements Corrected after Cure of HCV?

Eun Ju Cho

Seoul National Univ., Korea

Hepatitis C virus (HCV) has been associated with several metabolic derangements, including altered glucose homeostasis, and increased cardiovascular risk. The advent of direct-acting antivirals (DAAs) has allowed us to explore the potential reversal of metabolic derangements after cure of HCV.

HCV infection induces insulins resistance (IR) in the liver and peripheral tissues. Accordingly, IR is observed in 30-70% of individuals with chronic hepatitis C (CHC), correlating with a 67% higher risk for patients to develop type 2 diabetes mellitus (T2DM) in comparison to control subjects. The cure of HCV lead to improvements in insulin sensitivity and a reduced incidence of T2DM in patients undergoing DAA therapy. Furthermore, studies indicate that DAAs-treated patients experienced reduced occurrences of cardiovascular disease and stroke in comparison to untreated patients. Combined effects on atherosclerosis, IR and oxidative stress are proposed as the mechanisms behind this outcome. While studies have reported varying perspectives on the long-term impact of DAAs on renal outcome, many studies suggest a distinct trend marked by a decrease in glomerular filtration rate while on DAAs, followed by an improvement after the treatment. Despite the relatively short follow-up periods of the studies, this trend suggests a potential for long-term renal function improvement due to DAA therapy.

HCV alters the host lipid metabolism, and induces hepatic steatosis, hypobetalipoproteinemia, and hypocholesterolemia. Several studies have shown an increase in total cholesterol and low-density lipoprotein (LDL) cholesterol following treatment with DAAs. Considering the cardiovascular risk associated with chronic HCV infection, the increase in LDL cholesterol levels following treatment with DAAs raises concerns about cardiovascular implications. Therefore, careful monitoring of lipid levels and use of lipid-lowering agents are recommended.

In summary, while the cure of HCV can lead to improvements in metabolic derangements, the extent of correction may vary, and some metabolic alterations may persist even after viral clearance. Further research is needed to fully understand the long-term effects of HCV cure on metabolic health.

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Effects of DAA Treatment on Extrahepatic Manifestations in HCV Infection

Hyun Phil Shin

Kyung Hee Univ., Korea

HCV infection related morbidity

Chronic hepatitis C virus (HCV) is primarily causes fibrosis that can lead to cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[1] HCV is hepatotropic antibody but also associated with extrahepatic manifestations. Chronic HCV infection can cause various disorders, including cryoglobulinemic vasculitis, lymphoma, cardiovascular diseases, and type 2 diabetes (Table 1), and these diseases affect morbidity, mortality, and quality of life of the patients.[2] The different phenotypes of extrahepatic manifestations. HCV infection may be the results of multiple pathogenetic processes.

Effects of DAA treatment

The treatment regimen that directly interfere with HCV replication could provide opportunity for cure.[3] The use of the direct-acting antiviral agents (DAAs) made sustained virologic response (SVR) achievable. Sustained viral clearance is associated with low risk of extrahepatic manifestations of HCV infection. A sustained virologic response after HCV treatment lower the risk of cryoglobulinemic vasculitis and B-cell non Hodgkin's lymphoma (B-NHL), cardiovascular disease, and insulin resistance.[4]

Because, in addition to liver related complications, extrahepatic manifestations are threatening for patients, it is important to treat almost all patients with HCV infection before diseases progression. In the latest international guidelines such as the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, immediate treatment is recommended if there are significant extrahepatic manifestations of hepatitis C.[5,6]

In this session, we discuss to evaluate the effects and benefits of the cure of HCV infection on extrahepatic manifestations of CHC patients.

Table 1. Extrahepatic Manifestations of Hepatitis C Virus (HCV) Infection

Organs/systems	Extrahepatic manifestations
Lymphoproliferative disorders	- Mixed cryoglobulinemic vasculitis - B-cell non Hodgkin's lymphoma (B-NHL)
Cardiovascular disease	- Myocardial infarction, Coronary artery disease - Stroke, Peripheral arterial disease - Myocarditis, Coronary vasculitis - Heart failure.
Chronic kidney disease	- Chronic kidney disease - Membranoproliferative glomerulonephritis - Membranous nephropathy, - Tubulointerstitial injury
Endocrine	- Insulin-resistance - Type 2 Diabetes - Hypothyroidism
Nervous and Psychiatric	- Neurocognitive impairment - Depression
Miscellaneous	- Sicca syndrome - Chronic fatigue

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DAY 3 | Saturday, Sept. 23, 2023

Symposium 3-1. Occult Hepatitis Virus Infection and Post-Cure Virologic Failure

Chairs:

Patrick Kennedy (Queen Mary Univ. of London, UK)
Kwan Sik Lee (CHA Univ., Korea)

A Twist to a Cure of HCV Infection: Occult HCV Infection

Atsumasa Komori

Nagasaki Univ., Japan

Occult hepatitis C virus (HCV) infection (OCI) is generally defined as the presence of the HCV genome in either liver tissue or peripheral blood mononuclear cells (PBMCs), despite constant negative results for HCV RNA in serum. Detection of negative strand RNA, a signature of viral replication, solidify occult viral presence, discarding the possibility of passive transfer. Clinically, it might be worrisome reason of persistent serological and histological abnormality after sustained viral response (SVR). Moreover, it could matter with regard to the late relapse after SVR. The occurrence of OCI remains controversial in the last two decades[1], as it depends on the methods of detection being employed.

Even in the era of direct acting antivirals (DAAs), there were still reports that tried to resolve outstanding questions about OCI. Elmasry et al investigated the stringent OCI, with the detection of negative strand viral genome by high-sensitive Taqman qRT-PCR assay, among 14 patients with abnormal levels of serum aminotransferases despite SVR12 to DAAs for HCV infection after liver transplantation (n=129)[2]. OCI were detected in 3 and 2 patients in the liver and PBMCs, respectively, The lower (+)/(-) RNA strand ratio that was revealed in OCI samples, might be the result of defective virion assembly, leading to the reservoir of HCV-RNA within the infected cells. On the other hand, among immunocompetent hosts, Wang et al detected HCV RNA *in situ* by RNAscope assay in the liver of 13 SVR24 patients (9 and 4 after DAA and pegylated interferon+ ribavirin; PR, respectively) (n=130) and found that OCI was significantly linked with severity of fibrosis and active inflammation at post-SVR[3]; HCV relapse was documented in one of the OCI patients at 48 weeks after the end of PR treatment.

On the road to HCV elimination that ultimately leads to HCC suppression, is OCI still a twist to a cure of HCV infection at post-SVR? It remains uncommon, but might be substantial obstacle, that could lead us to re-examine optimal treatment and following up-scenario.

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Re-Infection of HCV Post-SVR

Ki Tae Yoon

Pusan National Univ., Korea

The development and availability of highly effective, well tolerated interferon-free direct-acting antiviral (DAA) therapy has revolutionized HCV therapeutics and provides the therapeutic tools required to strive for elimination. One challenge to achieving HCV elimination through therapeutic intervention is reinfection.

Reinfection with HCV occurs when an individual who has previously cleared the virus or achieved a sustained virologic response (SVR) following treatment becomes infected with a different viral strain.

Key factors contributing to HCV reinfection risk include high-risk behaviors, inadequate harm reduction strategies, and evolving viral quasispecies. Studies suggest that reinfection rates can be substantial in certain populations, highlighting the need for targeted prevention and education efforts.

The implications of HCV reinfection extend beyond individual health, as they also impact HCV transmission dynamics and the feasibility of HCV elimination programs. Effective prevention strategies, including needle exchange programs, access to clean injecting equipment, and pre-exposure prophylaxis, have shown promise in reducing reinfection rates.

People at risk for reinfection are recommended to have at least annual HCV RNA testing. Given the high observed reinfection incidence (particularly those with repeated infection) and short median time to reinfection posttreatment, more frequent monitoring should be considered, providing an opportunity for early intervention and interruption of transmission.

A comprehensive understanding of reinfection dynamics is crucial for optimizing public health interventions and achieving the ultimate goal of HCV elimination.

Occult HBV Infection: The Fate and Clinical Implications

Man-Fung Yuen

The Univ. of Hong Kong, Hong Kong

Occult hepatitis B infection (OBI) is defined by undetectable serum HBsAg by conventional assays with detectable serum and/or intrahepatic HBV DNA. It can further be classified as sero-negative (absence of anti-HBc/ anti-HBs) and sero-positive (presence of anti-HBc and/or anti-HBs) OBI. OBI patients originated from 3 main groups of patients namely, with history of acute hepatitis B infection, with chronic hepatitis B (CHB) with subsequent HBsAg seroclearance and with no known history of hepatitis B infection. Although, the liver biochemistry and histological severity in OBI patients are usually normal or mild, detectability of viral materials e.g. HBV DNA, cccDNA and integrated HBV DNA is universal in the livers. Patients with CHB with HBsAg seroclearance before the age of 50 have favourable outcome with decreased risk of hepatocellular carcinoma (HCC), cirrhosis and liver-related mortality. Integration of HBV DNA into host genome is the main drive for hepatocarcinogenesis in majority of patients with cryptogenic HCC. Another important clinical scenario occurs in OBI patients is reactivation of HBV with upsurge of viral replication potentially causing liver decompensation due to severe disease flares. Use of anti-CD 20 monoclonal antibody e.g. rituximab and receipt of haematopoietic stem cell transplantation leading to intense immunosuppression are notorious for HBV reactivation in HBsAg-negative, anti-HBc positive patients. Prophylactic antiviral treatment would prevent HBV reactivation in these patients and is associated with good outcome.

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Threat: HBV Reactivation after Resolved Hepatitis B

Su Jong Yu

Seoul National Univ., Korea

The reactivation of Hepatitis B virus (HBV) in individuals with a history of resolved infection presents a significant and often underestimated threat. This article aims to delve into the complexities surrounding HBV reactivation in the context of resolved HBV status, with a particular focus on the intricacies of diagnosis and management, including the occurrence of HBsAg seroreversion.

Resolved HBV status signifies controlled and latent viral infection, characterized by undetectable circulating HBV DNA levels and often normal liver function. Serological markers, such as antibodies against hepatitis B core antigen (anti-HBc), and occasionally antibodies against hepatitis B surface antigen (anti-HBs), denote prior exposure to the virus. However, it's crucial to recognize that resolved HBV status is not immune to disruption. HBV reactivation is a syndrome characterized by the reappearance of HBV particles in patients with previously resolved HBV or an increase in HBV viremia in patients with previously inactive chronic hepatitis B (CHB). HBV reactivation can occur spontaneously when the delicate equilibrium between viral suppression and immune control is disturbed. Still, it is more frequently triggered by specific diseases or conditions, including HIV/AIDS, cancer, diabetes, malnutrition, internal medicine specialties (such as rheumatology and gastroenterology), and certain inherited diseases affecting the immune system (e.g., congenital agammaglobulinemia and congenital IgA deficiency). In addition, it may be induced by specific medications or therapies, including immunosuppressive drugs, anticancer drugs, radiation therapy, stem cell transplantation, or organ transplantation. Reactivation can manifest as mild, asymptomatic increases in serum HBV DNA or severe hepatitis, potentially culminating in acute liver failure and death.

The diagnosis of HBV reactivation in individuals with resolved status demands heightened vigilance. Regular monitoring of serological markers, including HBsAg, HBV DNA levels, and anti-HBc, during immunosuppressive treatment is pivotal. HBsAg seroreversion is a distinctive aspect of HBV reactivation in individuals with resolved HBV status. It refers to the reappearance of hepatitis B surface antigen (HBsAg) in the serum of individuals who had previously tested negative for HBsAg. This phenomenon underscores the need for vigilance in monitoring serological markers during immunosuppressive treatment or chemotherapy. The detection of HBsAg seroreversion, along with increases in serum HBV DNA levels, is a critical indicator of reactivation. Prompt identification of reactivation allows for timely initiation of antiviral therapy. Particularly in regimens involving rituximab or other B-cell-depleting agents, antiviral therapy should be initiated concurrently with immunosuppression or chemotherapy. Prophylactic antiviral therapy should be sustained for at least six months post-immunosuppression or chemotherapy cessation and for at least 12 months if rituximab or other B-cell-depleting agents were administered. Periodic monitoring of se-

rum HBV DNA is advisable during and after prophylactic antiviral therapy. All hematopoietic stem cell transplantation (HSCT) recipients should undergo testing for HBsAg, anti-HBc, and anti-HBs before transplantation and are recommended to commence prophylactic antiviral therapy at the time of transplantation, continuing for a minimum of 12 months post-HSCT. The choice of antiviral agents depends on various factors, such as serum HBV DNA levels, the duration and intensity of immunosuppression or chemotherapy, and concurrent medical conditions. Agents like entecavir, tenofovir (DF or AF), and besifovir are preferred for long-term treatment.

In conclusion, HBV reactivation in resolved HBV cases, including the occurrence of HBsAg seroreversion, is a multifaceted issue that necessitates meticulous diagnosis and management. Vigilant monitoring, timely intervention, and appropriate antiviral therapy, along with the recognition of seroreversion, are indispensable components of effective care for individuals at risk of reactivation, ensuring the preservation of liver health in this vulnerable population.

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Keynote Lecture 3. What Happens to the Liver after a Cure of Viral Hepatitis?

Chairs:

Man-Fung Yuen (The Univ. of Hong Kong, Hong Kong)
Marc G. Ghany (NIH, USA)

cccDNA and HBV Functional Cure Is cccDNA the Chicken or the Egg?

Robert G. Gish

Hepatitis B Foundation, USA

Treatment of chronic hepatitis B virus (HBV) infection continues to evolve as we expand treatment guidelines to treat all with HBV-DNA+ to help prevent hepatocellular carcinoma (HCC), cirrhosis, death, liver transplant, infectivity, other linked cancers, and extrahepatic manifestations. To reach our next major milestone of functional cure (HBV-DNA {-} and hepatitis B surface antigen [HBsAg] {-}) at a rate greater than 40% with 1 year or less to treatment, we need to directly or indirectly effect covalently closed circular DNA (cccDNA) levels and transcriptional activity. The major discussion point relates to which comes first: cccDNA decline then HBsAg decrease or HBsAg change that results in decline of cccDNA Current evidence suggests that this can go in either direction or in parallel depending on the mechanism of action of the medication/treatment and also interaction of the virus and the immune system. Some publications, such as that seen with capsid assembly modulators (CpAM/CAMS), believe that reduction of capsid formation results in less recycling of complete capsids to the nucleus and falling replenishment of cccDNA and that cccDNA is then cleared naturally by endonucleases. Conversely, if we attack cccDNA directly with therapeutic endonucleases, using ARCUS or CRISPR technology as well as epigenetic modifiers (including histone modifiers), we can degrade cccDNA and help or directly effect HBV functional cure. With nucleoside or nucleotide treatment, functional cure is rare, but when seen there is a parallel concomitant reduction in HBsAg and cccDNA levels and activity. According to a recent study, for example, interferon produces a prolonged and sustainable reduction of transcription of cccDNA potentially through modifying the epigenetic alteration of cccDNA mini-chromosomes. Interferon for the near term will be part of many treatment protocols in the drug development pipeline such as the recent study by VIR Biotechnology with interferon, a monoclonal antibody, and an iRNA treatment that resulted in ~30% sAg loss on treatment and ~15% durable response off treatment. There are many other enzyme systems, including host enzymes that are supportive and permissive for cccDNA persistence that could the target of new therapies for HBV.

Theoretically, TLR activation including TLR7 and 8, should effect changes in cccDNA but to date, in the human setting, minimal changes in HBsAg have been identified. The process of epigenetic gene splicing may be used to cure HBV infection. Epigenetic therapy should be able to suppress the cccDNA mini-chromosome indefinitely, leading to a functional cure. This method includes chemically altering DNA without affecting the genetic code and minimizing off target effects. cccDNA methylation and cccDNA acetylation of mini-chromosome are two examples of epigenetic changes. Histone acetyltransferases and lysine/DNA/arginine methyltransferases are two of the most important epigenetic regulators of HBV-DNA. According to studies, histone deacetylase inhibitors can decrease cccDNA in duck HBV, and may enter human studies in the future.

In summary, the cccDNA story and HBsAg clearance leading to functional cure are partners in our goal to have finite therapies for HBV and lead to the downstream benefits of less HCC, cirrhosis, liver failure, infectivity, reactivation, and extrahepatic manifestations of HBV as well as WHO goals for HBV elimination.

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HBV Integration as a Novel Biomarker and Barrier to a Cure for HBV Infection

Patrick Kennedy

Queen Mary Univ. of London, UK

CHB remains the leading cause of hepatocellular carcinoma (HCC) worldwide and numbers of HBV-related HCC are expected to increase significantly in the coming decades. Clonal hepatocyte expansion and HBV DNA integration into the human genome are key events in hepatocarcinogenesis, but our understanding of these events in disease progression is limited. Beyond liver cancer, localisation of integrants suggest these events are not restricted to carcinogenesis, but also involved in mechanisms regulating hepatocyte metabolism and antiviral/inflammatory responses. In this talk, I will discuss immunological data in the context of the disease phases in CHB and age-related changes in the host immune response. I will dissect our current understanding of the host immune response and the complexity of its interaction with HBV and the viral reservoir. In addition, I will demonstrate the presence of clonal hepatocyte expansion and HBV DNA integration across the disease phases, which are factors which should be considered in the timing of treatment initiation, but may also represent barriers to functional cure.

In addition, I will discuss HBV DNA integration in those patients who currently do not meet treatment criteria, who are also at risk of disease progression and HCC development, and review the latest data emerging in the field. While this may represent a springboard for broadening treatment candidacy, I will also address the implications of HBV DNA integration as a barrier to cure and how we might overcome this. Finally, I will propose strategies that we can employ today to prevent disease progression and the complications of CHB in the future.

Immune Reconstitution after HCV Clearance with Direct Antiviral Agents

Tatsuya Kanto

National Center for Global Health and Medicine, Japan

DAA therapy has enabled HCV elimination in hepatitis C patients, but the control of post-SVR carcinogenesis in patients with advanced liver fibrosis remains a challenge. Natural killer (NK) cells play an important role in antitumor immunity, but their function is impaired in patients with chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). In addition, many patients with hepatitis C are elderly, thus age-related immune alterations should be considered. In order to elucidate the impact of HCV on immune cells including NK cells, we investigated their phenotypes and functions and compared them before and after DAA therapy, taking into account the impact of aging.

Peripheral immune cells and NK cell frequency, expression of 37 surface markers including active and inhibitory receptors and immune checkpoint molecules were evaluated by mass cytometry (CyTOF). Cytotoxic activity and ADCC activity were evaluated before treatment and at SVR12. As controls, 42 healthy adults in their 20s to 80s were analyzed, and the age- and sex-matched groups were used for comparison.

In the healthy controls, the expression of PD-1, ILT2, Siglec-10, and CD57 in CD56dimNK increased with age, and the expression of NKp46, Siglec7, and CD160 decreased, respectively. In the HCV group, the expression of activating receptor 2B4 was lower, while those of inhibitory receptors ILT2 and Siglec10 were higher than those in the age-matched controls. The cytotoxic and ADCC activity of NK cells in the HCV group, especially in ILT2-positive CD56dimNK cells, were impaired compared to those in the controls. After attaining the SVR, the frequency of T cells (CD4, CD8), regulatory T cells, MAIT cells, B cells, NK cells, and dendritic cells (mDCs, pDCs) did not change. The expression of ILT2 on pDCs, mDCs and monocytes was decreased after DAA treatment. However, the expressions of ILT2 and Siglec10 on NK cells and their cytolytic activity did not change even after SVR. Such phenotype and functional impairment of NK cells was observed as well in patients who developed post-SVR HCC.

In summary, ILT2 and Siglec10 are involved in the impairment of NK cell function due to aging and persistent HCV infection, the profiles of which are not fully recovered after DAA therapy. Longitudinal observation is warranted for the clarification of the link between "functional scar" of NK cells and post-SVR HCC.

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State-of-the-Art Lecture 3

Chair:
Shiv Kumar Sarin (Institute of Liver & Biliary Sciences, India)

A Roadmap to Eliminating Viral Hepatitis

Norah Terrault

Univ. of Southern California, USA

Viral hepatitis is a leading cause of morbidity and mortality worldwide. The availability of highly effective means to prevent and treat hepatitis B and C have made the global elimination of viral hepatitis an achievable goal – one that is endorsed by all WHO member states. To reach the 2030 targets of reducing hepatitis-related mortality by 65% and new infections by 90% reduction, a multi-layer strategy is essential. Key elements on the roadmap to elimination of viral hepatitis include:

- Public awareness and destigmatization
- National strategy
  - o Infrastructure support -- re-purposing the infrastructure used during the pandemic (testing platforms, workforce for testing and vaccination)
  - o Negotiating for low-cost diagnostics and antivirals
- Low-cost, high quality diagnostics, including point-of-care tests
  - o Pathways for diagnostic test development/approval vary by country and a more streamlined process
- Vaccination and prevention of mother-to-child transmission
  - o Primary intervention for HBV; recent inclusion of HBV vaccine
- Workforce capacity building
  - o To implement a "test and treat" approach, there is need to meet patients "where they are", a front-line workforce may be trained and supported to do diagnosis and treatment
- Simplification of treatment
  - o Minimal testing for diagnosis and staging (FIB-4) to support "test and treat" approach
- Access to low-cost therapeutics
- Surveillance of all steps on the cascade of care

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DAY 3 | Saturday, Sept. 23, 2023

Debrief Session

Chair:
Jeong Won Jang (The Catholic Univ. of Korea, Korea)

Viral Hepatitis Debrief

Hye Won Lee

Yonsei Univ., Korea

Non-Viral Liver Disease Debrief

Pil Soo Sung

The Catholic Univ. of Korea, Korea

Wrap-Up

Jeong Won Jang

The Catholic Univ. of Korea, Korea

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Symposium 3-2. Precision Medicine for the Cure of Viral Liver Disease

Chairs:

W. Ray Kim (Stanford Univ., USA)
Joon Hyoek Lee (Sungkyunkwan Univ., Korea)

Personalized Management of Viral Hepatitis of the Present and the Future

Maria Buti Ferret

Hospital Universitario Valle Hebron, Spain

Substantial progress has been made in the treatment of viral hepatitis in the last 15 years. There are currently seven approved drugs for the treatment of hepatitis B: two formulations of interferon (IFN) - conventional and pegylated IFN (PEG-IFN), and five nucleos(t)ide analogues - lamivudine, telbivudine, adefovir, entecavir, and tenofovir. Only three of them are currently recommended for therapy of hepatitis B. These drugs can suppress hepatitis B virus (HBV) replication, decrease hepatic inflammation and fibrosis and even reverse cirrhosis, prevent complications of cirrhosis, and re-duce the incidence of hepatocellular carcinoma (HCC). However, currently approved drugs do not eradicate HBV and have low rates of clearance of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) and HCC continues to occur at a lower rate. Patients with CHB are an heterogenous population that can benefit of personalized medicine as an approach to classify individuals into subpopulations that differ in their, rate of disease progression, and response to specific treatments. Therefore, the goal of personalized medicine is to provide optimal care according to the individual patient's disease characteristics, personal preference, comorbidities, and social circumstances such that maximum benefit can be derived while minimizing costs and adverse reactions. In hepatitis B, international society guidelines provide frameworks for managing patients with hepatitis B but these guidelines have to be inter-preted in the context of the individual patient's clinical and social circumstances. Personalized management of hepatitis B can be to guide the frequency and intensity of monitoring including HCC surveillance and urgency of treatment. It can also be applied to decisions on when to start treatment, which drug to use, and when to stop based on the individual patient's disease characteristics, preference, comorbidities and other mitigating circumstances. Another aspect of personalized medicine is that patients can benefit of minimizing costs and adverse reactions. IN the future with the new drugs in the pipeline, personalized medicine will continues playing an important role with the incorporation of biomarker suc as HBsAg levels, HBV RNA and core related antigen (HBcrAg) In viral hepatitis C, the high rates of Response, almost 100% achieved Sustained virologic response with 8-12 weeks of oral antivirals prevents the use of personalized medicine.

Risk Stratification for HCC in Chronic Hepatitis B: A Promise for Precision Medicine

Won Sohn

Sungkyunkwan Univ., Korea

Hepatitis B virus (HBV) infection is a global health concern that causes acute and chronic infections that can progress to liver cirrhosis, hepatocellular carcinoma (HCC), and liver failure, with eventual death. To increase the early detection of HCC, reduce complications among the patients with chronic hepatitis B (CHB), and improve overall survival. HCC surveillance is recommended for CHB patients with high-risk group which consisted of cirrhosis or Asians aged over 40 years. This is because the annual incidence of HCC in Asian patients with CHB irrespective of cirrhosis begins to exceed 0.2% after age 40 when surveillance for HCC is cost-effective.

The risk of HCC in CHB depends on viral activity (HBeAg, HBV DNA), disease activity (ALT level), fibrotic burden, and host factors (age, gender, family history, diabetes, alcohol, and smoking). The prediction of HCC risk in patients with CHB has been stratified using the risk score models based on above-mentioned factors.

Risk prediction scores for HCC in untreated patients

Most of risk prediction scores for HCC in untreated patients were derived from Asian cohorts. Host factors (age and gender) were included in all models in untreated patients. Fibrotic burden was also included in all models. However, fibrotic burden was assessed in various method such as presence of cirrhosis, platelet count, albumin level, liver stiffness measurement (LSM), and spleen size. Viral factors (high level of HBV DNA, and HBeAg positivity), and disease activity (high level of ALT) were included in the risk prediction model in untreated patients. The accuracy of prediction for HCC development over 5-10 years ranged between 0.76 and 0.92, which was presented by the area under the receiver operating characteristic curve (AUROC).

Risk prediction scores for HCC in patients receiving antiviral agents

Nowadays, use of oral antiviral agents (nucleos(t)ide analogue, NA) has been established as the standard treatment for CHB. The use of antiviral agents suppresses HBV replication and decreases hepatic inflammation. Furthermore, long-term use of antiviral agents can improve advanced fibrosis or cirrhosis in the histologic findings. There is no question about the role of preventive effect of antiviral agents on the reducing risk of HCC in patients with CHB. The use of antiviral agents significantly reduces the risk of HCC in CHB compared to patients with no use of antiviral agents.

There are several prediction models for HCC risk in CHB patients receiving antiviral agents. Most of them were derived from Asia, but PAGE-B model was made based on Caucasian patients. Host factors (age and gender) and fibrotic burden were included in all models in CHB patients receiving antiviral agents. Some models included However, viral factors (HBV DNA, and HBeAg), and disease activity (ALT) are not included in

the models with use of antiviral agents. The AUROC for HCC development over 5-10 years ranged between 0.76 and 0.86.

Factors to consider in more accurate risk model

To establish more accurate risk model on HCC prediction in patients with CHB, several factors can be included in the next models. Although it's unclear at the moment, several risk factors for HCC risk will be elucidated in patients with CHB. Recently, metabolic abnormalities were associated with HCC development. Obesity, diabetes, and hepatic steatosis/steatohepatitis can be clarified whether those factors are included in the risk prediction models. Also, novel biomarkers for HBV (HBcrAg or HBV RNA) will be evaluated as risk factors for HCC. In CHB patients receiving antiviral treatment, the change of fibrotic burden after HBV suppression will be considered as a risk factor together with fibrosis status at pre-treatment.

Conclusion

Risk stratification for HCC in patients with CHB has been approached based on viral factor, host factor, disease activity, and fibrotic burden. The risk prediction model should be applied considering the use of antiviral treatment. For precision medicine such as a different strategy of HCC surveillance, several risk factors will be clarified by the advanced in medicine.

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Host and Genetic Factors for Precision Medicine towards a Cure of Viral Hepatitis

Kazuaki Chayama

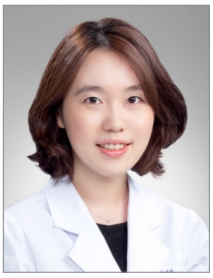
Hiroshima Univ, Japan

In recent years, significant progress has been made in the analysis of single nucleotide polymorphisms (SNPs) using genome-wide association studies (GWAS). These studies have revealed crucial associations between specific SNPs and human phenotypes, including susceptibility to chronic viral infections, response to drug therapy, and risk of adverse events. Among viral infections, chronic hepatitis B virus (HBV) infection stands out as one of the most prevalent infectious liver diseases, particularly in the Asia-Pacific region. While comprehensive preventative measures, such as the administration of concentrated anti-HBs gamma globulin to infants, followed by vaccination, have reduced carrier rates in many Asian countries, some areas still report carrier rates as high as 15 percent.

Through a two-stage genome-wide association study, we have identified a significant association between chronic hepatitis B and 11 SNPs located within a region that includes HLA-DPA1 and HLA-DPB1. Subsequently, we have identified both risk haplotypes (HLA-DPA10202-DPB10501 and HLA-DPA10202-DPB10301, OR= 1.45 and 2.31, respectively) and protective haplotypes (HLA-DPA10103-DPB10402 and HLA-DPA10103-DPB10401, OR = 0.52 and 0.57, respectively).

Another significant association was uncovered between SNPs near the IFNL3 (IL28B) locus and the response to interferon-based therapy for chronic hepatitis C virus (HCV) infection. Patients with specific SNP genotypes, such as rs8099917 and rs12979860, exhibited a higher rate of virus eradication when treated with peg-interferon and ribavirin therapy. These SNPs were later found to be associated with spontaneous virus clearance. In the current era, ribavirin-induced anemia remains a major cause of discontinuation and dose reduction during anti-hepatitis C virus therapy. Our investigation into predictive factors for anemia in hepatitis C virus patients treated with combination therapy has identified a significant association with the SNP rs1127354, located upstream of the inosine triphosphate pyrophosphatase gene on chromosome 20p13.

While these findings are scientifically intriguing, the significance of SNP analysis has diminished in light of the remarkable efficacy of drugs such as direct-acting antivirals against HCV and nucleos(t)ide analogues for HBV. Current interest in SNP analysis is now primarily directed toward understanding the development of hepatocellular carcinoma in patients in whom viral replication is well controlled. Further studies are warranted to advance our understanding of and ability to prevent and predict the occurrence of hepatocellular carcinoma in the future.



Biomarker Discovery and Application for Liver Disease in the Era of Precision Medicine

Sun Young Yim

Korea Univ., Korea

The precision medicine emerged after the unraveling of the DNA blue-print of the human genome representing a paradigm shift in the "one-size-fits-all" medical model. Development of the molecular biology-omic technologies known as: genomics, epigenomics, metagenomics, transcriptomics, proteomics, and metabolomics has provided substantial omic data (Big Data) of the human population. The precision medicine had focused on the management of complications in advanced stages but there is a shift towards the early detection of liver damage.

In fatty liver disease, PNPLA3 variant was associated with increased hepatic fat and NAFLD disease severity, while TM6SF2, GCKR and HSD17B13 were involved in the genetic susceptibility of the disease. Polygenic risk scores (PRSs) are theoretically designed to explain the relative risk of a disease, as these scores provide information on how a person compares with others with different genetic susceptibility background. In the case of NAFLD and NASH, PRSs could be conceptually very advantageous not only for allowing early disease detection, but also for implementing timely actionable measures. Invasive diagnostic approaches, such as liver biopsy, as well as early pharmacological intervention, would be advised for high-risk populations whereas low-risk individuals (i.e., those on the left-tail of the curve) would be monitored until clinical risk becomes evident. For those deemed at low or medium risk, which probably applies to the large majority of the affected patients, lifestyle changes would be advised, including regular physical activity and dietary modifications aimed at optimizing body weight and controlling the key metabolic risk factors. However, the reproducibility and replication of genetic variants of NAFLD across diverse populations around the world is insufficient and the effect sizes of most of the variants are yet to be established.

Despite the improvement in early HCC detection and the advancement in treatment over the past decades, the 5-year overall survival rate of HCC is still dismal at about 20%. Given the survival benefit of diagnosing HCC at early stages amenable to potentially curative treatment, current clinical practice guidelines recommend regular HCC screening in patients who are at risk of chronic liver disease. To address the limitations in the current HCC screening and improve its effectiveness, performance of the risk stratification and early detection tests should be improved by integrating multi-modal information including molecular variables. As indicators of genetic susceptibility to HCC, SNPs have been studied extensively in the settings of genome-wide association study or hypothesis-driven single-gene analysis.

Chronic liver diseases, caused by viral hepatitis (with exception of hepatitis C), alcohol consumption, obesity-related non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are etiologies that cannot be solely treated or cured with pharmacological regimens to date. Thus, a personalized-medicine approach embracing both the genetic

susceptibility and lifestyle factors such as nutrition, physical activity and mental health could be an option for patients, mainly at early stages of diagnosis.

Recent developments of clinical, molecular and imaging-based tools to address the current challenges in liver disease and approaches of their clinical translation and implementation will be discussed.

APASL STC 2023 BUSAN

Asian Pacific Association for the Study of the Liver Single Topic Conference

"Toward Elimination of Viral Hepatitis"

September 21-23, 2023 | BEXCO, Busan, Korea

DAY 3 | Saturday, Sept. 23, 2023

Early Morning Workshop 3. Fibrosis Regression after Antiviral Therapy in Patients with Chronic Viral Hepatitis

Chair:
Atsumasa Komori (Nagasaki Univ., Japan)

Fibrosis Regression after HCV Treatment and Its Clinical Significance

Jeong-Ju Yoo

Soonchunhyang Univ., Korea

In recent decades, substantial progress has been made in the field of hepatology, particularly in the management of chronic hepatitis C virus (HCV) infection. Chronic HCV infection is a major global health concern, affecting millions of individuals and often leading to severe liver complications, including cirrhosis and hepatocellular carcinoma. One of the key challenges posed by chronic HCV infection is the development of liver fibrosis, a complex pathological process characterized by the excessive accumulation of extracellular matrix proteins within the liver tissue. Fibrosis not only impairs liver function but also serves as a precursor to end-stage liver diseases, making its regression a critical therapeutic goal. The introduction of direct-acting antiviral agents (DAAs) has revolutionized the landscape of HCV treatment. These agents, with their remarkable efficacy and improved safety profiles, have significantly increased the rates of sustained virological response (SVR) and have become the cornerstone of HCV management. However, beyond their antiviral effects, there is emerging evidence suggesting that successful HCV treatment with DAAs might also lead to the regression of liver fibrosis.

The regression of liver fibrosis after HCV treatment holds immense clinical significance. Not only does it reflect a potential halt in disease progression, but it also offers the possibility of restoring lost liver function and reducing the risk of developing end-stage complications. Despite the growing body of research on this topic, there remains a need to comprehensively understand the mechanisms underlying fibrosis regression, the factors influencing its occurrence, and its long-term implications for patient outcomes. This lecture will provide a comprehensive overview of the current state of knowledge regarding fibrosis regression following HCV treatment. It will delve into the molecular mechanisms that drive fibrosis resolution, explore the clinical evidence supporting the concept, discuss potential predictors of fibrosis regression, and highlight the implications for clinical practice and patient management.

Clinical Implication of On-Therapy Fibrosis Regression in Chronic Hepatitis B

Mi Na Kim

Yonsei Univ., Korea

Chronic hepatitis B (CHB) is prevalent liver disease worldwide, and is a leading cause of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality. Although long-term viral suppression is available by rapid advances in antiviral therapy (AVT), achieving complete sterilizing cure is not yet possible. Thus, the risk of disease progression and HCC development has not been completely eliminated even though long-term AVT, especially in patients with advanced liver fibrosis or cirrhosis.

Fibrotic burden is the most critical predictor of prognosis in CHB. Long-term AVT with potent nucleos(t)ide analogues has shown to be associated with significant improvement of liver necroinflammation and fibrosis by suppressing hepatitis B virus (HBV) replication. Long-term AVT has been shown to be associated with significant histological improvement, even in patients with HBV-related cirrhosis.

Several studies have focused on the association of fibrosis regression with long-term prognosis in patients with CHB using noninvasive assessment of fibrosis. In the multi-center study conducted in Korea, the achievement of subcirrhotic liver stiffness (LS) after AVT was independently associated with a decreased risk of HCC development. In a large cohort of Caucasian patients with CHB, elastographic reversion at 5 years of AVT defined by LS value <12 kPa significantly decreased the subsequent HCC risk. Our group also demonstrated that achieving subcirrhotic LS at 5 years of AVT was independently associated with lower risk of HCC development beyond 5 years of AVT.

In this lecture, we will review the fibrosis regression after potent AVT, and the related clinical impact in patients with CHB.

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DAY 3 | Saturday, Sept. 23, 2023

Early Morning Workshop 4. Screening and Prognosis of HDV Infection with Case Discussion

Chair:

Jose D. Sollano (The Univ. of Santo Tomas, Philippines)

Threat: Who Should Be Screened for HDV Infection? - Case Presentation

Hee Yeon Kim

The Catholic Univ. of Korea, Korea

Guidelines vary on whom to test for HDV infection (eg, AASLD employs a risk-based approach, whereas EASL advocates screening for all individuals with positive HBsAg). Due to the risk of HDV superinfection, HBsAg-positive individuals with high-risk behaviour or living in countries or communities with high HDV prevalence should undergo repetitive testing or whenever they experience episodes of aminotransferase elevations or liver disease decompensation that cannot be attributed to other causes.

Recent investigations showed that a risk-based screening strategy neglects a substantial portion of HDV cases. Notably, anti-HDV screening remains an infrequent practice among carriers of positive HBsAg, even in countries where it is recommended for all HBsAg-positive individuals.

Here, we present a case involving the superinfection of HDV in patients HBV-related liver cirrhosis. A-50-year-old woman visited local clinical due to elevated levels of aminotransferase. She had a history of hepatitis B but had not been receiving any medication for it. She reported abstaining from alcohol consumption and refraining from using any herbal medicines. The initial examination revealed the presence of liver cirrhosis, with ALT levels at 149 U/L, HBeAg negative, and HBV DNA at 464 IU/mL. Subsequently, she commenced treatment with tenofovir alafenamide. After a duration of 12 months on tenofovir alafenamide, her HBV DNA became undetectable. However, there was no reduction observed in her liver enzyme levels. She was referred to our clinic 12 months after initiating the tenofovir alafenamide treatment.

At the 12-month mark of receiving tenofovir alafenamide treatment, her HBV DNA remained undetectable. However, her laboratory findings were as follows: AST/ALT 133/34 IU/L, total bilirubin 0.98 mg/dL, albumin 3.8 g/dL, and platelet 130,000/μL.

Additionally, the HDV RT-PCR test yielded a positive result, and liver biopsy indicated cirrhosis with severe lobular and portoperiportal activity. As part of a compassionate use initiative in Korea, she was subsequently administered bulevirtide.

After 6 months of receiving bulevirtide, her HDV RNA became undetected, and there was a notable decrease in AST/ALT levels (53/43 IU/L). She is currently continuing with bulevirtide treatment, and we have scheduled a rebiopsy to be conducted at the 12-month mark of her bulevirtide regimen.

Who Should Be Screened for HDV Infection?

Jae Hyun Yoon

Chonnam National Univ, Korea

The Hepatitis D virus (HDV) is a defective virus that requires the presence of the Hepatitis B virus (HBV) to complete its life cycle. HDV utilizes all three HBV envelope proteins, known as HBV surface antigen, to both enter and exit the hepatocyte and maintain its productive infection. HDV can infect susceptible hosts through coinfection with HBV or by superinfecting chronic HBV carriers. Coinfection with HBV and HDV may result in the clearance of both viruses, but it typically leads to acute hepatitis, with a wide clinical spectrum ranging from asymptomatic or mild hepatitis to acute liver failure. Severe cases of acute hepatitis are more prevalent in HBV/HDV coinfection than in primary HBV mono-infection. HDV superinfection of HBV patient leads to chronic hepatitis D and it is related to worse outcome than HBV mono-infection with more aggressive progression to cirrhosis.

Three recent large-scale meta-analyses have reported the prevalence of HDV infection to be between 0.11% and 0.98% in the general population, between 4.5% and 13.02% in all HBsAg-positive carriers, and between 14.6% and 18.6% among individuals attending hepatology clinics.[1-3] Derived from previous studies, the estimated global burden of individuals living with serological evidence of HDV exposure ranges from 12 to 72 million. The wide variation in the estimated global prevalence of HDV infection, diagnostic limitations and the lack of effective treatments were key hurdles. Recent studies showed that risk-based screening misses a sizeable number of HDV cases and that anti-HDV screening is performed in a minority of HBsAg-positive carriers even in countries where it is recommended for all HBsAg-positive individuals.[4-6] These findings underline the need to increase clinicians' awareness of the importance of testing for anti-HDV among HBsAg-positive carriers.

The implementation of reflex testing for anti-HDV in all individuals who tested positive for HBsAg resulted in a 5-fold increase in the diagnosis of HDV infections. The majority of anti-HDV-positive individuals were young, with 60% not exhibiting common risk factors for infection and 60% having advanced fibrosis.[7] These findings support the argument for universal anti-HDV screening in HBsAg-positive individuals, as early diagnosis of HDV infection is crucial for providing personalized counseling and reducing the risk of transmission to anti-HDV negative HBV carriers.

The prevalence of anti-HDV is higher among selected high-risk populations. A reported prevalence of 15% has been observed in patients co-infected with the human immunodeficiency virus (HIV), 30% in institutionalized individuals, and up to 67% in people who inject drugs (PWID). A recent systematic review and meta-analysis has shown that the prevalence of anti-HDV is higher in hemodialysis recipients, men who have sex with men, and patients who test positive for anti-hepatitis C virus (HCV) antibodies.[3]

In summary, it is recommended that all HBsAg-positive individuals undergo screening for anti-HDV antibodies at least once using a validated assay.

Additionally, due to the risk of HDV superinfection, HBsAg-positive individuals who engage in high-risk behavior or reside in countries or communities with high HDV prevalence should undergo repeated testing or be tested whenever they experience aminotransferase flares or liver disease decompensation that cannot be otherwise explained.

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Prognosis of HDV: Risk Factors and Whom to Treat

Lubna Kamani

Liaquat National Hospital, Pakistan

Hepatitis Delta Virus (HDV) is a single stranded RNA virus comprising of 17,000 nucleotides. It is an incomplete or defective virus, and it relies on Hepatitis B Virus (HBV) three envelope proteins to enter and replicate within hepatocytes for infectivity.[1] Within the infected host nucleus it utilizes host RNA polymerase II for replication and is independent of HBV. HDV can infect as a co-infection with HBV or super infection in HBV carriers. Former leads to acute hepatitis and sometime fulminant hepatic failure whereas latter converts into more chronic state with increased risk of cirrhosis, decompensation and hepatoma.[2]

Important risk factors for HDV are[3,4]: In order of greatest risk

a) People who inject drugs (PWID)
b) Commercial sex workers
c) Men who have sex with men (MSM)
d) Patients with HCV, HIV and cirrhosis.
e) Patients on hemodialysis
f) Migrant from endemic countries
g) No HBV vaccination administered and rarely via vertical transmission.

Screening for anti-HDV antibodies by validated essay should be performed in all HBsAg positive individuals at least once and can be re-tested whenever clinically indicated.[5] Prognosis depends upon stage of liver disease, increase necro-inflammatory markers, persistence of HDV viremia,[6] high HBV DNA and presence of other virus co-infections. Progression of liver disease also depends upon other factors like alcohol, obesity and diabetes.[7] All patients with active HDV should be considered for treatment unless there is a contraindication.[5] All HDV with compensated cirrhosis should be considered treatment with PegINFα preferably for 48weks.[8] Treatment prolongation to 96 weeks does not increase virological response but liver histological improvement were noted in most patients.[9] Bulevirtide (formerly Myrcludex B) received conditional authorization by EMA for use in HDV. It blocks the attachment of HBsAg to the cell entry receptor NTCP. It should be considered for the long term use in compensated cirrhosis at the dose of 2 mg daily. In the absence of contraindications to PegINFα combined treatment with Bulevirtide may be considered till robust literature becomes available.[5] Frequent monitoring by CBC, LFT, HBV DNA, HDV RNA, ultrasound and liver stiffness needs to be done during and after treatment.

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Plenary Presentation

P-01

The Epidemiology of Hepatitis B Virus Infection in an Endemic Region: A 15-Year Analysis and the Impact of COVID-19

Jin Wook Park[2], Log Young Kim[1*], Jeong-Ju Yoo[2*], Young Chang[3], Hoongil Jo[4], Young Youn Cho[5], Sangheun Lee[6], Dong Hyeon Lee[7‡], Jae Young Jang[3‡]

[1]Department of Big DATA Strategy, National Health Insurance Service, Wonju, Korea, [2]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea, [3]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, South Korea, 4Department of Internal Medicine, Wonkwang university school of medicine &hospital, 5Department of Internal Medicine, Chung-Ang University Hospital, 6Department of Internal Medicine, Catholic Kwandong University College of Medicine, 7Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, South Korea

Aims: The purpose of this study is to investigate the epidemiological changes in chronic hepatitis B (CHB) and assess the impact of COVID-19 over the past 15 years in South Korea, a region endemic to hepatitis B virus (HBV).

Methods: We utilized the National Health Insurance Service claims data of hepatitis B patients spanning from 2007 to 2021. Furthermore, to compare the characteristics of the hepatitis B group, we established a 4-fold control group adjusted for age and gender through propensity score matching analysis.

Results: Excluding the COVID period, the number of patients with CHB has consistently increased over the past 15 years. The average age of the CHB patient group has shown a yearly rise, while the prevalence of male dominance has gradually diminished. Additionally, there has been an upward trend in the proportion of patients receiving antiviral drugs, observed in both men and women. When categorized based on the severity of liver disease, the proportions of hepatocellular carcinoma (HCC), liver cirrhosis, and decompensation have exhibited a declining pattern, whereas the proportion of liver transplants has continuously risen. Patients with CHB have demonstrated significantly higher medical and medication costs compared to the control group, particularly when complications such as decompensation, HCC, or liver transplantation have developed. Moreover, patients with CHB have shown a higher prevalence of comorbidities such as osteoporosis, chronic kidney disease, and diabetes compared to the control group, along with a significantly higher rate of concomitant medication usage. During the COVID period, the HBV group experienced a substantial decrease in the number of outpatient visits and overall medical costs compared to the control group.

Conclusions: The epidemiology of chronic hepatitis B in HBV endemic areas has undergone significant changes over the past 15 years, encompassing shifts in prevalence, severity, medical costs, and comorbidities. Furthermore, the impact of COVID-19 has been observed to decrease healthcare utilization among patients with chronic hepatitis B when compared to controls.

Keywords: HBV, Epidemiology, COVID-19 infection

P-02

The Single-Cell Landscape Identifies Immunophenotyping and Tumor Microenvironments of HBV-Positive and Negative Hepatocellular Carcinoma

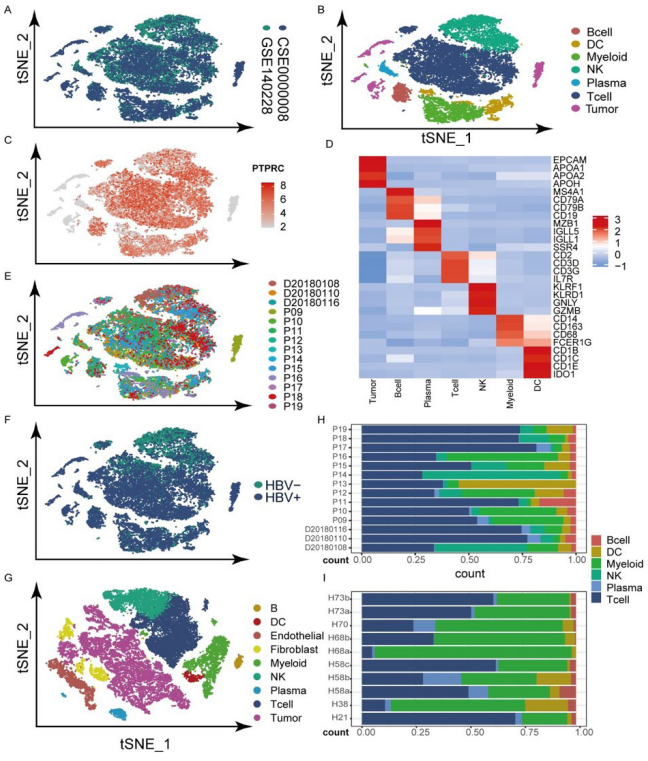
Hongping Xia

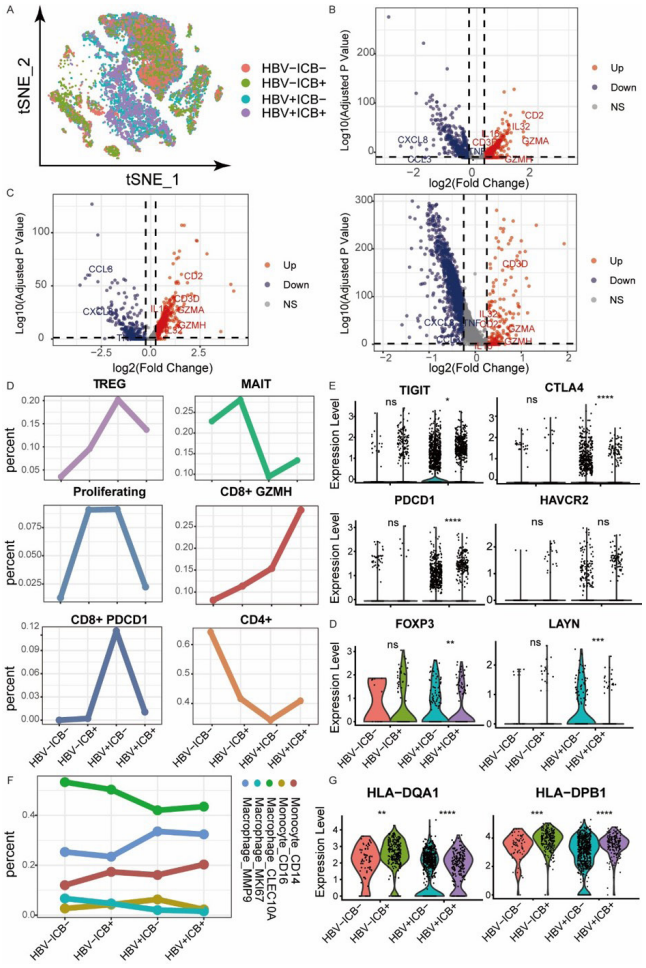
Laboratory of Cancer Genomics, National Cancer Centre, Singapore

Aims: HBV infection leads to hepatocellular carcinoma (HCC) and affects immunotherapy. Exploring tumor ecosystem in HCC help to gain a deeper understanding and design more effective immunotherapy strategies for HCC patients with or without HBV infection.

Methods: Single-cell RNA sequencing (scRNA-seq) series were integrated as a discovery cohort to interrogate the tumor microenvironment (TME) of HBV+ HCC and HBV- HCC. We further dissect the intratumoral immune status of HBV+ and HBV- HCC. An independent cohort, including samples treated with immune checkpoint blockade therapy (ICB), was used to validate the major finding and investigate the effect of HBV infection on response to immunotherapy.

Results: The interrogation of TME indicated that TREG, exhausted CD8+ T cell and M1-like Macrophage_MMP9 were enriched in HBV+ HCC, while MAIT was enriched in HBV- HCC. All subclusters of T cells showed high expression of immune checkpoint genes in HBV+ HCC. TREG cells enriched in HBV+ HCC also showed more robust immunosuppressive properties, which was confirmed by crosstalk between immune cell subsets. The ability of antigen presentation with major histocompatibility complex (MHC)-II was down-regulated in HBV+ HCC and this phenomenon can be reversed by immunotherapy. Two types of HCC also present different responses to immunotherapy.





Conclusions: There is a more immunosuppressive and exhausted TME in HBV+ HCC than in HBV- HCC. This in-depth immunophenotyping strategy is critical to understanding the impact of HBV along with the HCC immune microenvironment and helping to develop more effective treatments in HCC patients.

Keywords: Single-cell landscape, Tumor microenvironments, Immunophenotyping, Hepatitis B virus laboratory of cancer genomics, National cancer centre, Singapore

P-03

An Increase in the Number of Activated Regulatory T Cells Is Associated with an Improvement in Liver Function of Patients with Severe Alcoholic Hepatitis after Steroid Therapy

Min Woo Kang[1], Soon Kyu Lee[1,2], Jung Hyun Kwon[1,2], Soon Woo Nam[1,2], Jeong Won Jang[1,3], Ji Won Han[1,3], Jong Young Choi[1,3], Seung Kew Yoon[1,3], Pil Soo Sung[1,3*]

[1] The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2] Division of gastroenterology and hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3] Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Regulatory T cell (Treg cell) is known to suppress immune response by inhibiting T cell proliferation and cytokine production. Alcoholic hepatitis is common, but the role of T reg cells in alcoholic liver is poorly understood. Here, we investigated $CD4^+$ $CD25^+$ $Foxp3^{high}CD45RA^-$ effector Treg cell population in the peripheral blood of alcoholic hepatitis patients and compared with clinical data.

Methods: 33 patients with alcoholic hepatitis were consecutively enrolled from two academic hospitals (Seoul St. Mary's Hospital, Incheon St. Mary's Hospital) in this study. Among 33 patients, 12 patients had severe alcoholic hepatitis treated with steroid (steroid group) and the others (n =1) had mild alcohol-induced liver injury without steroid treatment (no steroid group). Peripheral blood mononuclear cells (PBMCs) were isolated from patients at the time of enrollment and 7 days after treatment. Frequency of $CD4^+CD25^+Foxp3^{high}CD45RA^-$ effector Treg cell was examined by flow cytometry and compared between the steroid and no steroid group. Moreover, we evaluated the population of activated Treg cells according to the steroid treatment response. Single cell RNA sequencing analysis using paired PBMCs was also performed and compared between before and after steroid treatment. The proliferation of CD4 T cells and CD8 T cells after steroid treatment was performed using Carboxyfluorescein diacetate succinimidyl ester (CFSE) labelling. The phenotype change of Treg cells after steroid treatment *in vitro* was examined by flow cytometry.

Results: Patients who had treated steroid showed poor liver function compared to non-treated patients at baseline. Effector Treg cell population was significantly expanded in steroid-treated patient group whereas it was not in non-treated group. Among the steroid group, steroid responders (n=9) showed significant increase in the population of effector Treg cells after steroid therapy. Additionally, the correlation between the decrease in MELD score (Model for End-Stage Liver Disease) and the amount of effector Treg cell increase was statistically significant. In the single cell RNA sequencing analysis using paired PBMCs (pre- and post- steroid therapy), we found that cytokine production and type I IFN gene signature in CD4 T cells were downregulated after steroid therapy, suggesting the possible protective roles of expanded activated Treg cells. The CFSE rate decreased in both CD4 T cells and CD8 T cells after steroid treatment. The effector Treg population was increased after steroid treatment *in vitro*.

Conclusions: Thus, our data suggest that the increased frequency of suppressive Treg cells in peripheral blood may be associated with improvement of liver function in alcoholic hepatitis.

Keywords: Regulatory T cell, Alcoholic hepatitis, Steroid

P-04

Liver Failure versus Organ Failure in Acute on Chronic Liver Failure: Sequence and Consequence

Young Chang, Soung Won Jeong, Jae Young Jang*, Tae Hyung Kim, Hyung Joon Yim, Eileen L. Yoon, Seong Hee Kang, Hee Yeon Kim, Jeong-Ju Yoo, Baek Gyu Jun, Sung Won Lee, Jung Gil Park, Hyun Chin Cho, Tae Yeob Kim, Do Seon Song, Sung-Eun Kim, Ki Tae Suk, Young Kul Jung, Moon Young Kim, Sang Gyune Kim, Won Kim, Jin Mo Yang, Dong Joon Kim, on behalf of the Korean Acute-on-

Chronic Liver Failure (KACLiF) Study Group

[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Korea, [3]Department of Internal Medicine, Hanyang University Seoul Hospital, Seoul, Korea, [4]Department of Internal Medicine, Yonsei University Wonju Severance Christian Hospital, Wonju, Korea, [5]Department of Internal medicine, Uijeongbu St. Mary's Hospital, the Catholic University of Korea, Uijeongbu, Korea

Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea, [6]Department of Internal Medicine, Ulsan University Gangneung Asan Hospital, Gangneung, Korea, [7]Department of Internal Medicine, Yeungnam University Hospital, Daegu, Korea, [8]Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea, [9]Department of Internal Medicine, New Hope Internal Medicine Clinic Seoul, Korea, [10]Department of Internal medicine, St. Vincent's Hospital, the Catholic University of Korea, Suwon, Korea, [11]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea, [12]Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, Korea, [13]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University, Boramae Medical Center, Seoul, Korea

Aims: Acute-on-chronic liver failure (ACLF) is a syndrome characterized by acute decompensation of chronic liver disease or cirrhosis associated with organ failures, resulting in high short-term mortality. This study aimed to determine the sequence and consequences of organ failures, particularly hepatic and renal failure, and to identify their impact on short-term survival rates in ACLF patients.

Methods: We extracted 340 ACLF patients from the prospective Korean Acute-on-Chronic Liver Failure cohort. Timing of organ failure, especially hepatic failure and renal failure, was assessed and overall survival was compared according to organ failure sequence. Overall survival (OS) was estimated by Kaplan-Meyer survival analysis with log-rank test and multivariate survival analysis was conducted with Cox proportional hazards model.

Results: Compared to the group without hepatic failure, the OS was worse in the group manifested by initial hepatic failure (adjusted hazard ratio [aHR]=3.6; p=0.008), and in the group with hepatic failure during the disease period (aHR=5.7; p=0.002). There was no difference in OS between the group without renal failure and the group manifested by initial renal failure (aHR=0.8, p=0.51), but the group with renal failure during the disease period showed a poor prognosis (aHR=1.9, p=0.056). Initial renal failure only group had significantly longer OS than initial hepatic failure group (aHR=10.8, p=0.02).

Conclusions: Organ failure that develops during hospitalization is more fatal than organ failure that manifested initially. ACLF manifested with initial renal failure has better prognosis than with initial hepatic failure. ACLF with initial renal failure show a great prognosis with 28-day survival rate of over 90%, but the prognosis is dismal if renal dysfunction develops during hospitalization.

Keywords: Acute on chronic liver failure, Renal failure, Hepatic failure

Free Paper Presentation

Free Paper Presentation 1. [Viral Liver Disease]

FP-01

Positive Rates of Autoantibodies in Chronic Hepatitis C Patients before and after DAA Therapy: A Prospective, Multicenter Study in South Korea

Su Hyun Choi[1]*, Gwang Hyeon Choi[1]*, Eun Sun Jang[1], Youn Jae Lee[2], Young Seok Kim[3], In Hee Kim[4], Sung Bum Cho[5], Byung Seok Lee[6], Kyung-Ah Kim[7], Woo Jin Chung[8], Sook-Hyang Jeong[1]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea, [2]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea, [3]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea, [4]Department of Internal Medicine, Jeonbuk National University Hospital, Jeonju, Republic of Korea, [5]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, [6]Departments of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea, [7]Departments of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang Republic of Korea, [8]Departments of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea

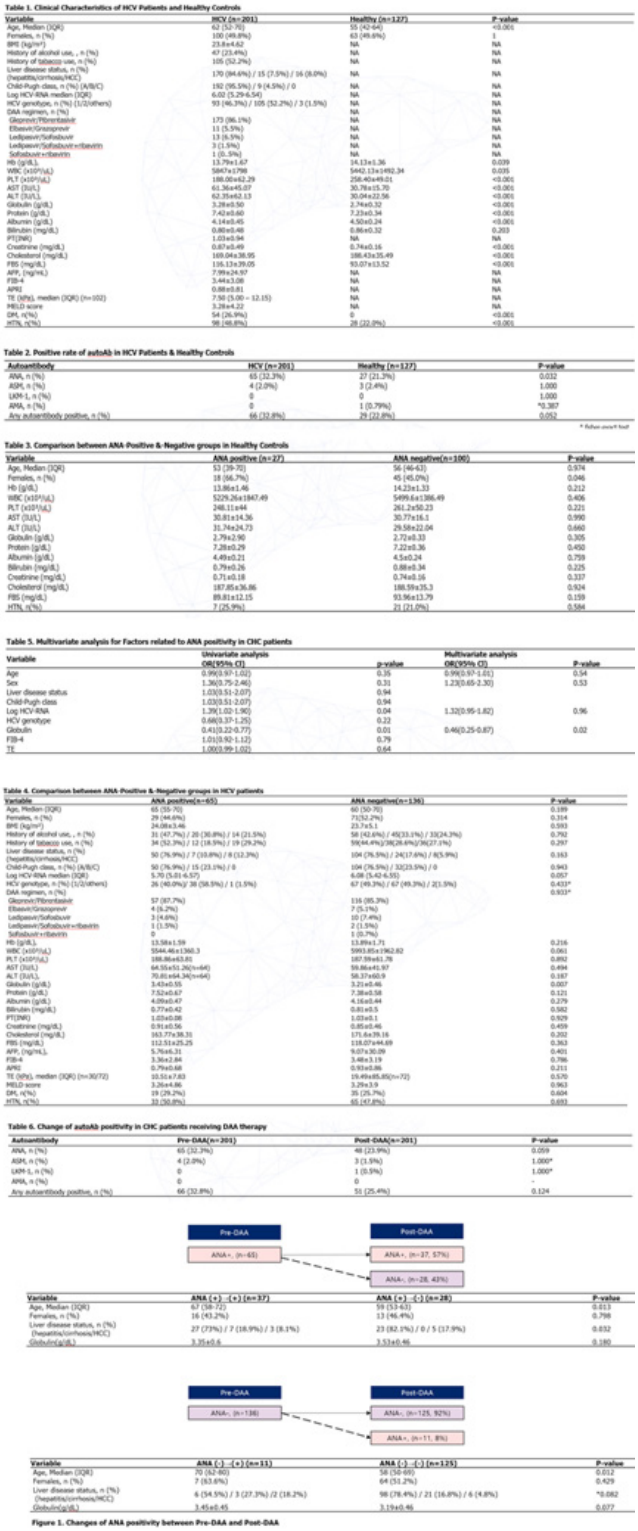
Aims: Hepatitis C Virus (HCV) infection causes extrahepatic diseases, involving B-cell dysregulations and autoantibody (autoAb) production. This study aimed to investigate the positive rates of 4 conventional autoAbs (anti-nuclear, anti-smooth muscle, anti-LKM type1, and anti-mitochondrial; ANA, ASM, Anti-LKM1, and AMA, respectively) in the patients with chronic HCV infection (CHC) at pretreatment (PreTx) and sustained virological response (SVR) 12 weeks after direct acting antiviral (DAA) therapy.

Methods: Using a prospectively collected plasma obtained from 201 CHC patients (median age 62, 49.8% of female, 7.5% of cirrhosis) enrolled in 8 hospitals before and after DAA therapy, ANA, ASM, Anti-LKM1, and AMA were detected by indirect immunofluorescence. As a control group, plasma samples from 127 healthy person representative of age and sex standardized Korean adult population (median age 55, 49.6% of female) were obtained from a biobank.

Results: The positive rate of ANA in CHC patients was significantly higher than that in healthy controls (32.3% vs 21.3%, p=0.032), however ASM (2.0% vs 2.4%), LKM1 (0% vs 0%), and AMA (0% vs 0.79%) were not. In CHC patients, ANA positivity at PreTx tended to decrease at SVR (32.3% vs 23.9%, p=0.059) In healthy controls, ANA positivity was higher in females than males regardless of age, while in CHC patients, ANA positivity was not associated with sex, but higher globulin level.

The 37 (57%) patients among 65 ANA-positive CHC at PreTx maintained positive at SVR, and 11 (8%) patients among 136 ANA-negative CHC at PreTx converted positive at SVR. In CHC patients who maintained or converted ANA-positive at SVR, were older (67 vs 59, p=0.013) with higher proportion of cirrhosis or HCC (27% vs 17.9%, p=0.032).

Conclusions: Pretreatment ANA positivity in CHC patients was 32.3%, which tend to decrease after SVR. However, the positive rate of ASM, anti-LKM1, and AMA was negligible.



Keywords: HCV, Autoantibody, ANA

FP-02

Prediction of Long-Term HBsAg Seroclearance after Entecavir Cessation in Chinese Hepatitis B Patients with the Novel Alanine-Aminotransferase to Quantitative-HBsAg Ratio

Rex Wan-Hin Hui[1], Ryan Hin-Man Leung[1], Lung-Yi Mak[1,2], Kevin Sze-Hang Liu[1], Danny Ka-Ho Wong[1,2], James Fung[1,2], Wai-Kay Seto[1,2,3], Man-Fung Yuen[1,2]

[1]Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, [2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong SAR, [3]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Aims: Nucleos(t)ide analogue cessation in chronic hepatitis B (CHB) may induce HBsAg seroclearance. Good predictors at end-of-treatment (EOT) to predict long-term HBsAg seroclearance are needed.

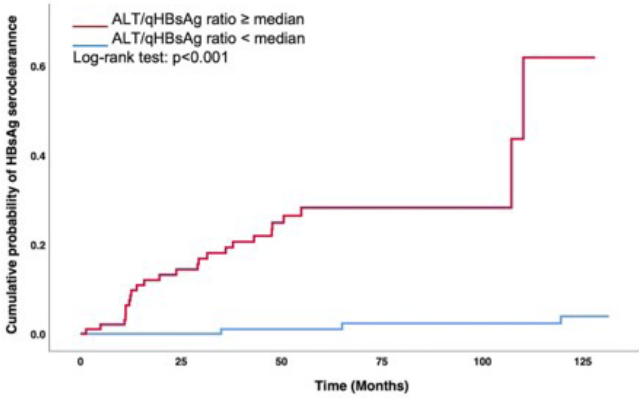
Methods: This study followed-up Chinese CHB patients from two studies of entecavir cessation from Hong Kong. The first study (n=80) did not have inclusion criteria for quantitative HBsAg (qHBsAg), and the second (n=114) recruited patients with qHBsAg <200 IU/ml. All patients were non-cirrhotic, HBeAg negative, with undetectable HBV at EOT. They had close monitoring for 48 weeks with regular HBV DNA, qHBsAg and ALT measurements, and were resumed on entecavir if HBV DNA >2000 IU/ml. After 48 weeks, the patients were reviewed every 6 months.

Results: 194 patients (63.4% male, median age 55.6, on entecavir for a median of 47.2 months) were recruited. The median ALT and qHBsAg at EOT were 23.0 (18.0-31.0) U/L and 104.5 (30.8-616.0) IU/ml respectively. 151 (77.8%) patients developed HBV DNA>2000 IU/ml and were resumed on entecavir by week 48. After follow-up for 70.7 (51.0-118.2) months, 28 (14.4%) patients had HBsAg seroclearance at 29.3 (12.3-47.7) months after EOT. EOT qHBsAg predicted HBsAg seroclearance in univariate analysis (HR 0.993 [95% CI 0.989-0.998], p=0.007), and this association trended towards significance in multivariate analysis (HR 0.997 [95% CI 0.993-1.000], p=0.075), possibly due to the low and narrow EOT qHBsAg range limiting statistical power. EOT ALT (HR 1.029 [95% CI 1.000-1.059], p=0.049) and not resuming entecavir (HR 5.525 [95% CI 2.283-13.333], p<0.001) were predictors of HBsAg seroclearance in multivariate analysis. The ratio of ALT/qHBsAg (conceptually viewed as the intensity of immune-mediated response per IU/mL of HBsAg) at EOT and week 6 after EOT independently predicted HBsAg seroclearance (EOT: HR 1.007 [95% CI 1.001-1.012], p=0.018; Week 6: HR 1.033 [95% CI 1.015-1.052], p<0.001), regardless of whether entecavir was later resumed. The ALT/qHBsAg ratio at EOT and week 6 achieved area-under-curve of 0.800 (95% CI 0.736-0.854) and 0.879 (95% CI 0.812-0.928) in predicting HBsAg seroclearance respectively.

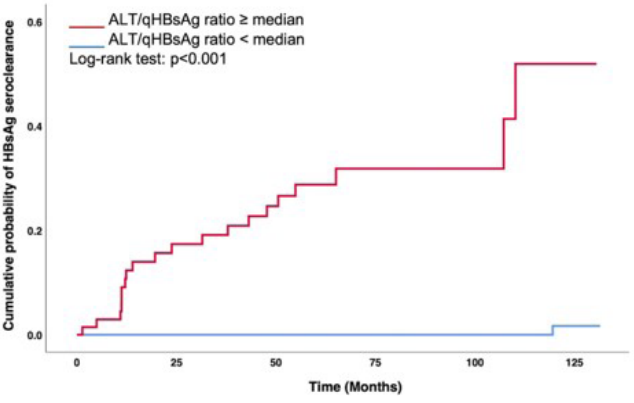
Conclusions: While further validation is warranted, the ALT/qHBsAg ratio is a novel marker that may aid prediction of long-term HBsAg seroclearance after entecavir cessation.

Keywords: HBV, Quantitative HBsAg, Functional cure, Treatment cessation, Finite therapy

Panel A- Cumulative probability of HBsAg seroclearance stratified by ALT/qHBsAg ratio at treatment cessation



Panel B - Cumulative probability of HBsAg seroclearance stratified by ALT/qHBsAg ratio at week 6 after treatment cessation



FP-03

Metabolic Effects of Antiviral Treatments in Patients with Chronic Hepatitis B

Hyunjae Shin, Yunmi Ko, Youngsu Park, Jeayeon Park, Moon Haeng Hur, Min Kyung Park, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Aims: It has been known that various antiviral treatments in patients with chronic hepatitis B (CHB) have distinct metabolic effects. Tenofovir alafenamide (TAF), an emerging therapeutic option among nucleos(t)ide analogues (NAs), has been recognized as worsening lipid profiles among people with human immunodeficiency virus (HIV). However, it was unclear whether TAF-induced dyslipidemia were also significant in patients with CHB.

Methods: We conducted a comprehensive study of all-comers with CHB over a 15-year period at a single tertiary center in South Korea. The study consisted of two parts: The single-antiviral and the switch-antiviral study. In the single-antiviral study, patients were evaluated at the initial center visit and divided into four groups: ETV-only

(n=5,082), TDF-only (n=3,292), TAF-only (n=625) and non-antiviral (n=14,551), according to the status of antiviral treatment. In the switch-antiviral study, patients who switched from NAs to TAF or from TAF to NAs were included (n=61). All patients' metabolic profiles (i.e., serum cholesterol, triglyceride, glucose and body weight) were obtained over time. The single-antiviral study utilized propensity score matching (PSM) method, and the switch-antiviral study utilized pairwise analyses to evaluate changes in metabolic profiles.

Results: In the single-antiviral study, changes in serum total cholesterol (median, -2.10 mg/dL/year in the TDF-only group and +0.67 mg/dL/year in the TAF-only group) and body weight (median, -0.15 kg/year in the TDF-only group and +0.39 kg/year in the TAF-only group) were noted. After PSM, there was a statistically significant difference in total cholesterol levels (median, -2.74 mg/dL/year in the TDF-only group and +1.08 mg/dL/year in the TAF-only group; both $p<0.001$) compared to the non-antiviral group. Moreover, after adjusting for key confounding variables, changes in total cholesterol levels were distinct between groups (median, -2.57 mg/dL/year in the TDF-only group and +2.88 mg/dL/year in the TAF-only group; $p=0.002$ and $p=0.02$, respectively) compared to the non-antiviral group. In the TDF-only group, HDL-cholesterol levels decreased (median, -0.55 mg/dL/year; $p<0.001$) compared to the non-antiviral group. In the switch-antiviral study, patients who switched NAs from TDF to TAF had a higher total cholesterol level after switching to TAF (median, +9.4 mg/dL/year) than before switching to TAF (median, -1.0 mg/dL/year; $p=0.047$).

Conclusions: TAF was associated with an increase in serum total cholesterol levels, whereas TDF was associated with a decrease in total cholesterol and HDL cholesterol, even after adjusting for changes in body weight and statin use. Statin use might delay the deterioration of lipid profiles. The development of dyslipidemia and associated outcomes should be monitored in patients with CHB and preventative treatment with statin might be required.

Keywords: Tenofovir alafenamide, Total cholesterol, LDL cholesterol, Chronic hepatitis B

FP-04

CAMP-B Score Predicts the Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B after HBsAg Seroclearance

Hye Won Lee*[1], Terry Cheuk-Fung Yip*[2,3,4], Vincent Wai-Sun Wong[2,3,4], Young-Suk Lim[5], Henry Lik-Yuen Chan[6], Sang Hoon Ahn[1], Grace Lai-Hung Wong[2,3,4], Jonggi Choi[5]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Department of Medicine and Therapeutics, [3]Medical Data Analytics Centre (MDAC), [4]Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, [5]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [6]Department of Internal Medicine, Union Hospital, Hong Kong

Aims: The risk of hepatocellular carcinoma (HCC) persists after hepatitis B surface antigen (HBsAg) seroclearance in patients with chronic hepatitis B (CHB). This study aimed to identify risk factors and construct a predictive model for HCC development.

Methods: We retrospectively analysed patients with CHB with HBsAg seroclearance. The primary outcome was HCC development. Factors identified from a multivariable Cox model in the training cohort, consisting of 3,476 patients from two Korean hospitals, were used to construct the prediction model. External validation was performed using data from 5,255 patients in Hong Kong.

Results: In the training cohort, HCC occurred in 102 patients during 24,019 person-years of observation (0.43%/year). Cirrhosis, age ≥50 years, male gender, and platelet <150,000 were independently associated with an increased risk of HCC in multivariable analysis. Risk scores were assigned to cirrhosis (C: 3), age ≥50 years (A: 2), male gender (M: 3), and platelet <150,000 (P: 1). The time-dependent AUROCs for 5, 10, and 15 years in the training cohort were 0.782, 0.817, and 0.825, respectively. In the validation cohort, 85 patients developed HCC (0.24%/year). The corresponding incidence of HCC in the low, intermediate, and high-risk groups were 0.07%, 0.37%, and 0.90%, respectively. The time-dependent AUROCs for 5, 10, and 15 years in the validation cohort were 0.785, 0.771, and 0.796, respectively.

Conclusions: CAMP-B score (cirrhosis, age ≥50 years, male gender, and platelet <150,000) were significantly associated with HCC development after HBsAg seroclearance. CAMP-B score can be easily implemented in real-world clinical practice and helps stratify the risk of HCC in patients with CHB following HBsAg seroclearance.

Keywords: Chronic hepatitis B, HBsAg seroclearance, Long-term clinical outcomes, Hepatocellular carcinoma

FP-05

Strategy on Hepatitis C Virus Elimination Focused on Economic Evaluation of Mass Screening in Korea

Hwa Young Choi[1], Kyung-Ah Kim[2], Bo Young Park[3], Bo Youl Choi[3], Moran Ki[1]

[1]Department of Cancer Control and Policy, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea, [2]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, [3]Department of Preventive Medicine, Hanyang University College of Medicine, Seoul, Korea

Aims: In 2021, WHO proposed the elimination of hepatitis C virus (HCV) targeting a reduced incidence rate of less than 5 per 100,000 and a reduced HCV related mortality rate of less than 2 per 100,000. The purpose of this study is to establish various HCV screening scenarios to achieve HCV elimination target in Korea, and to present the most efficient HCV screening scenario by evaluating the timing and economic feasibility of achieving the HCV elimination target with each scenario.

Methods: As of 2020, a virtual cohort was constructed with the entire population of 30-79 years old in Korea. The incidence and mortality of HCV and liver disease in this cohort were estimated for 20 years. For economic evaluation, the analysis model was constructed as a dynamic transmission model that includes simulation of HCV incidence by age accounting for not only patients at a specific time point but also newly emerging patients. In this study, a total of 16 HCV screening scenarios were constructed by combining 4 assumptions (Screening cycle, Screening rate, incidence reduction rate and antiviral treatment rate). The 16 different scenarios were built to evaluate whether each screening scenario reaches eliminating HCV targeting

a reduced incidence rate ≤5/per 100,000 and HCV related mortality rate mortality rate ≤2/per 100,000. With perspectives of the health care system including direct medical expenses, the economic evaluation for each scenario was performed through cost-utility analysis and cost-benefit analysis.

Results: Among 16 screening scenarios, 3 screening scenarios achieved the incidence and mortality targets within 20 years. The most quickly scenario of achieve is a scenario in which screening is conducted every 2 years assuming screening rate of 90%, antiviral treatment rate of 90%, and a 30% reduction in HCV incidence. This scenario achieved the incidence rate 5 years after the start of screening and the mortality rate target 18 years later (incidence rate was 4.86 per 100,000 and mortality rate was 2.00 per 100,000). Also, the result of the economic evaluation, Incremental Cost-Effective Ratio (ICER) was $ 8,445/QALY, and benefit-cost ratio (BCR) was 0.79, the cost effectiveness was high, but the cost benefit was low. The most economical scenario of achieve is a scenario in which screening is conducted every 4 years assuming screening rate of 90%, antiviral treatment rate of 90%, and a 30% reduction in HCV incidence. This scenario achieved the incidence rate 9 years after the start of screening and the mortality rate target 20 years later (incidence rate was 4.80 per 100,000 and mortality rate was 1.94 per 100,000). Also, the result of the economic evaluation, Incremental Cost-Effective Ratio (ICER) was $ 4,765/QALY, and benefit-cost ratio (BCR) was 1.53, the cost effectiveness and the cost benefit was high.

Conclusions: In this study, it was confirmed that HCV screening has the potential to reduce HCV incidence and the mortality related to HCV. In addition, the burden of disease and direct healthcare costs related to HCV can be also reduced by HCV screening. Therefore, the introduction of HCV screening is highly recommended. This study confirmed that if HCV screening is conducted six times every four years, the HCV removal goal can be achieved most economically after 20 years.

Keywords: Hepatitis C virus (HCV), WHO hepatitis C elimination target, Mass screening, Dynamic transmission model, Economic evaluation

FP-06

Antiviral Therapy and Risk for Hepatocellular Carcinoma after Hepatitis B Surface Antigen Seroclearance

Han Ah Lee[1], Hwi Young Kim[1], Beom Kyung Kim[2,3], Sang Hoon Ahn[2,3], Hyun Woong Lee[2], Ja Kyung Kim[2], Dong Hyun Sinn[4], Yeon Seok Seo[5], Seung Up Kim[2,3]

[1]Department of Internal Medicine, College of Medicine, Ewha Womans University; [2]Department of Internal Medicine, Yonsei University College of Medicine; [3]Yonsei Liver Center, Severance Hospital; [4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine; [5]Department of Internal Medicine, Korea University College of Medicine

Aims: The complete assessment of the association between prior antiviral therapy (AVT) and the risk of hepatocellular carcinoma (HCC) after HBsAg seroclearance has not been conducted. This study aimed to assess the relationship between AVT and HCC risk and develop a prediction model to determine the likelihood of HCC occurrence after HBsAg seroclearance. In addition, long-term incidence of HCC and hepatic decompensation after HBsAg seroclearance was investigated.

Methods: In total, 2,845 patients with chronic hepatitis B who achieved HBsAg seroclearance between 2003 and 2022 were retrospectively reviewed for eligibility. Exclusion criteria for this study included patients who developed HCC before HBsAg seroclearance, or had a follow-up duration of less than 6 months. The primary endpoint of the study was the occurrence of HCC, while the secondary endpoint was hepatic decompensation. Baseline characteristics of the patient groups were balanced using inverse probability of treatment weighting (IPTW).

Results: Among 1,521 patients selected for statistical analysis, 84.2% (n=1,280) achieved HBsAg seroclearance without AVT (spontaneous clearance group), while the remaining 15.8% (n=241) achieved it after AVT (AVT-induced clearance group). During a median follow-up of 4.3 years, 37 patients (2.4%) developed HCC after HBsAg seroclearance. AVT-induced clearance group had a significantly larger number of patients with alcohol consumption and cirrhosis, a lower platelet count, and a higher Albumin-Bilirubin (ALBI) grade compared to the spontaneous clearance group (all $p<0.05$). The incidence rate of HCC was comparable between the two groups ($p=0.727$ by log-rank test). However, after IPTW, that was significantly higher in the spontaneous clearance group compared to the AVT-induced clearance group ($p=0.014$ by log-rank test). In multivariate analysis, older age (aHR=1.054), cirrhosis (aHR=5.022), lower platelet count (aHR=0.992), ALBI grade ≥ 2 (aHR=5.340), and no previous AVT (aHR=0.461) were independent predictors for the higher risk of HCC development (all $p<0.05$). The prediction model developed using these variables for the HCC development after HBsAg seroclearance had AUC of 0.828 (95% CI 0.724□0.933) in the training group, and 0.801 (95% CI 0.719-0.882) in the validation group. The cumulative incidence of HCC was consistent 0-5 and 5-10 years after HBsAg seroclearance ($p=0.30$). In total, 98 patients (6.5%) developed hepatic decompensation after HBsAg seroclearance, and the cumulative incidence of decompensation was persistent 0-5 and 5-10 years after HBsAg seroclearance ($p=0.47$). In multivariable analysis, HBsAg loss for over 5 years was not associated with the risk of HCC (adjusted subdistribution hazard ratio [aSHR] 0.85, 95% CI 0.48-1.51, $p=0.580$) or hepatic decompensation (aSHR 0.79, 95% CI 0.52-1.19, $p=0.250$).

Table. Risk scores for HCC development after HBsAg seroclearance

Variable	β	HR	95% CI	P value	Risk score
Age					
≤45 years	reference				0
>45 years	2.263	1.054	1.023-1.087	0.001	2
Liver cirrhosis					
No	reference				0
Yes	1.959	5.022	2.372-10.636	<0.001	2
Platelet count, × 10^9/L					
<50	reference				0
≥50	-1.003	0.992	0.986-0.997	0.002	-1
ALBI grade					
1	reference				0
2 or 3	1.863	5.340	2.887-9.878	<0.001	2
Antiviral therapy					
No	reference				0
Yes	-0.715	0.461	0.256-0.830	0.010	-1

HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HR, hazard ratio; CI, confidence interval; ALBI, Albumin-Bilirubin

Conclusions: The novel prediction model based on age, cirrhosis, platelet count, ALBI grade, and history of AVT is beneficial for determining the risk of HCC after HBsAg seroclearance. The risk of HCC and decompensation is consistent over time after HBsAg seroclearance.

Keywords: HBsAg, Antiviral therapy, Hepatocellular carcinoma, Hepatitis B virus

Free Paper Presentation 2. [Non-Viral Liver Disease]

FP-07

Analysis of Immune-Related Adverse Events and Time-to-Treatment Discontinuation of Atezolizumab and Bevacizumab in Patients with Hepatocellular Carcinoma: A Multicenter Cohort Study

Heechul Nam[1,2], Jaejun Lee[1,2], Ji won Han[1,2], Soon Kyu Lee[1,2], Hyun Yang[1,2], Hae Lim Lee[1,2], Pil Soo Sung[1,2], Hee Yeon Kim[1,2], Myeong Jun Song[1,2], Jung Hyun Kwon[1,2], Chang Wook Kim[1,2], Soon Woo Nam[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2*]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]The Catholic Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

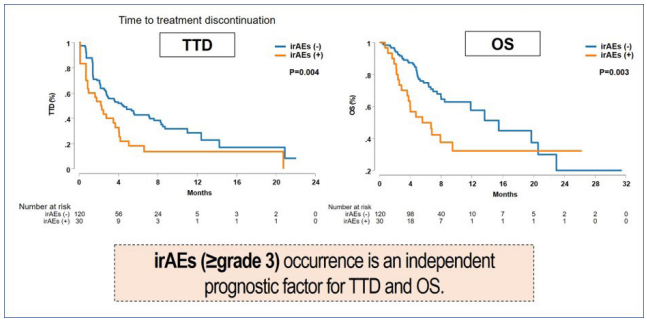
Aims: Pragmatic endpoints, such as time-to-treatment discontinuation (TTD), defined as the duration from starting a medication to the date of treatment discontinuation or death, have been proposed as a potential efficacy endpoint for real-world practice. This study aims to analyze the frequency and severity of immune-related adverse events (irAEs) and TTD in patients with hepatocellular carcinoma (HCC) receiving Atezolizumab and Bevacizumab (A+B) treatment.

Methods: This retrospective, multi-center study included consecutive HCC patients who received A+B treatment from September 2020 to December 2022. The primary endpoint of the study was the assessment of TTD and overall survival (OS). The associations of factors on outcomes were analyzed using Cox proportional hazards regression and multivariable logistic regression models.

Results: The study included 150 HCC patients with a median age of 64 years. 85.3% were male, and 69.3% had viral hepatitis etiology. 52% had portal vein tumor thrombus (PVTT). Overall, 34.0% patients experienced grade 3 or higher treatment-related adverse events, with 20.0% reported irAEs. The incidence rates of irAEs were hepatitis (9.3%), colitis (3.3%), severe fatigue (2.0%), pneumonitis (2.0%), cholangitis (1.3%), skin rash (1.3%), myositis (0.7%), asthma (0.7%), and anaphylactic shock (0.7%). The median OS was 13.6 months (95% CI, 8.0-20.6) and the median progression-free survival was 5.7 months (95% CI, 4.0-12.5), while the median TTD was 3.6 months (95% CI, 2.6-5.1). Occurrence of irAEs, female gender, ALBI grade ≥2, Child-Pugh class B, and neutrophil-to-lymphocyte ratio (NLR) ≥3 and were found to be significantly associated with poor TTD in the univariate analysis. In the multivariate analysis, occurrence of irAEs (HR, 1.765; 95% CI, 1.108-2.813, p=0.004), ALBI grade ≥2 (HR, 1.639; 95% CI, 1.054-2.550, p=0.028) and female gender (HR, 1.687; 95% CI, 1.018-2.795, p=0.042) were identified as the independent predictor of TTD. For OS, the univariate analysis showed that irAEs, ALBI grade ≥2, Child-Pugh class B, NLR ≥3, PVTT and tumor size (≥7cm) were found to be significant. The occurrence of irAEs (HR, 2.423; 95% CI, 1.371-4.280, p=0.002), ALBI grade ≥2 (HR, 2.926; 95% CI, 1.511-5.667, p=0.001), Child-Pugh class B (HR, 2.685; 95% CI, 1.258-5.308, p=0.005), and PVTT (HR, 2.029; 95% CI, 1.159-3.552, p=0.013) were identified as the independent predictor of OS.

Conclusions: In our multicenter retrospective cohort study, the combination therapy of A+B demonstrated significant efficacy. Our results highlight the importance of TTD as an important outcome measure, encompassing both disease progression and treatment discontinuation. We identified irAEs as an independent prognostic factor for A+B treatment. Thus, it is crucial to actively monitor and manage irAEs to optimize treatment outcomes.

Keywords: Hepatocellular carcinoma, Immune checkpoint inhibitor, Immune-related adverse events, Time-to-treatment discontinuation



FP-08

Long-Term Outcome of Wilson's Disease: Single Center Analysis of 361 Asian Patients

Hyo Jin Nam[1], Won-Mook Choi[2], Danbi Lee[2], Ju Hyun Shim[2], Kang Mo Kim[2], Young-Suk Lim[2], Han Chu Lee[2], Jonggi Choi[2]

[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: There are few data regarding long-term outcomes and survival of patients with Wilson disease (WD) from large Asian cohorts. We aimed to analyze the clinical long-term data in a large Korean cohort of WD.

Methods: Between 2000 and 2022, 361 patients with WD were retrospectively analyzed at Asan Medical Center, Seoul, Republic of Korea. Diagnosis of WD were made on typical symptoms, clinical, biochemical and genetic findings. Primary outcome was liver transplant-free survival. Development of hepatocellular carcinoma (HCC) in the entire patients and progression to liver cirrhosis (LC) in patients without LC at diagnosis were also analyzed. Patients who met the following criteria were excluded: 1) received liver transplantation within 6 months of diagnosis; 2) follow-up period less than 6 months; 3) co-infection with hepatitis B virus; 4) combined alcoholic liver disease. Median follow-up period was 13.0 years.

Results: The mean age was 17.2 years, and 206 (57.1%) of the patients were male. At diagnosis, 146 (40.4%) patients had LC, of which 48 (13.3%) patients showed decompensation. Transplant-free survival rates at 5-, 10-, 15-, and 20-years were 100.0%, 98.4%, 97.9%, and 97.9%, respectively. Cumulative probabilities of HCC development at 5-, 10-, 15-, and 20-years were 0.0%, 0.4%, 1.9%, and 6.1%, respectively. Of the 215 patients without LC at diagnosis, 15 (7.0%) patients showed progression to LC with cumulative risks of 0.0%, 3.0%, 6.1% and 14.1% at 5, 10, 15, and 20 years, respectively. No patients without LC at diagnosis died or developed HCC during the follow-up period. Older age and LC at diagnosis were significantly associated with a worse survival rate (p<0.05 for all).

Conclusions: Korean patients with WD had a favorable long-term prognosis However, older age and LC at the time of diagnosis increase the risk of death and HCC development.

Keywords: Wilson's disease, Long term outcome, Genetic disease

FP-09

Enhancing Early Hepatitis Diagnosis: Optimizing Decision Trees with Genetic Algorithms

Rifaldy Fajar[1], Caroline Zyah Virera[2]

[1]Department of Mathematics and Computer Science, Karlstad University, Sweden, [2]Department of Public Health, Karlstad University, Sweden

Aims: Liver disease is a serious global health concern caused by factors such as viral infections, bacterial infections, or exposure to toxic substances. Among the various liver diseases, hepatitis is particularly alarming and widespread. Unfortunately, hepatitis often goes unnoticed in its initial phases, leading to the development of chronic viral infections. To tackle this diagnostic challenge and enable early detection, this study focuses on enhancing the decision tree algorithm through the implementation of a genetic algorithm approach. By optimizing this algorithm, we aim to improve the prediction accuracy for early-stage hepatitis disease.

Methods: A comprehensive dataset of Hepatitis patients was obtained from Kaggle, serving as the secondary data source. Prior to analysis, the dataset underwent rigorous preprocessing, including handling missing values, feature selection, and data normalization. To enhance the performance of the decision tree model, a genetic algorithm was employed for optimization. The genetic algorithm utilized selection, crossover, and mutation operations to evolve a set of decision tree rules that maximized prediction accuracy. The optimized decision tree model was evaluated using various evaluation metrics, such as accuracy, precision, recall, and F1-score. To ensure unbiased evaluation, the dataset was divided into training and testing subsets using cross-validation techniques. A comparative analysis was conducted to assess the effectiveness of the genetic algorithm optimization by comparing the performance of the optimized decision tree model against the baseline decision tree model without genetic optimization.

Results: The study findings revealed that the genetic algorithm optimization significantly improved the accuracy of the decision tree algorithm in diagnosing Hepatitis disease. The initial accuracy of the decision tree algorithm was 64.30%. However, after optimization using the genetic algorithm, the accuracy increased to 89.30%, representing a substantial 25% improvement compared to the decision tree algorithm without genetic optimization.

Conclusions: The application of genetic algorithm optimization in the decision tree method demonstrated promising results for the early prediction of Hepatitis disease. By incorporating genetic algorithms, the accuracy, and effectiveness of the diagnostic algorithm were significantly enhanced, addressing the current gap in early detection of Hepatitis. The study's findings highlight the potential of this approach to facilitate timely intervention and reduce the risk of disease progression into chronic conditions. These results contribute to the growing body of research aimed at improving Hepatitis diagnosis and emphasize the importance of leveraging optimization techniques in predictive models for liver disease.

Keywords: Hepatitis, Genetic algorithms, Decision trees, Early prediction

FP-10

Bifidobacterium Breve and Longum Attenuate Western Diet Induced Non-Alcoholic Fatty Liver Disease

Sang Jun Yoon[1], Raja Ganesan[1], Haripriya Gupta[1], Sung-Min Won[1], Jin-Ju Jeong[1], Satya Priya Sharma[1], Dong Joon Kim[1], Moon-Young Kim[2], Yeon-Seok Seo[3], Sang-Gyune Kim[4], Ki Tae Suk[1]*

[1]Institute for Liver and Digestive Disease, Hallym University College of Medicine, [2]Department of Internal Medicine, Yonsei University Wonju College of Medicine, [3]Department of Internal Medicine, Korea University College of Medicine, [4]Department of Internal Medicine, Soonchunhyang University

Aims: Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of liver disease worldwide. However, definitive medical treatments have not been established apart from lifestyle modifications. Probiotics can be lucrative due to their availability, cost, and absence of severe side effects. This study aimed to elucidate the underlying mechanisms of western diet-induced NAFLD associated with the gut microbiome and explore the effects of *Bifidobacterium breve*, and *B. longum* from the gut microbiota profiles perspective.

Methods: Six weeks old C57BL/6J mice were fed the Western diet with/without probiotics for 8 weeks. *B. breve* and *B. longum* were administered at a concentration of 10^9 CFU/day. We compared liver/body weight ratio (L/B ratio), NAFLD activity score (NAS), and performed liver function tests with serum. We also conducted the histopathological examination, fecal analysis, and markers for inflammation, lipogenesis, and β-oxidation in the liver.

Results: Western diet induces NAFLD through dysbiosis caused by a reduction in *Bacteroidetes* and an increase in *Proteobacteria* and *Firmicutes* phyla. Probiotics groups shows significant results in liver enzymes (AST 113.1±34.1, p=0.005; ALT 64.4±25.83, p=0.04), L/B ratio (4.86±0.57, p<0.0001) and improved NAS (1.89±1.45, p=0.001) compared with the untreated group (AST 175.5±36.84; ALT 110±55.3; L/B ratio 7.07±0.75; NAS 5±1). Moreover, *Bifidobacterium* downregulated the expression of hepatic steatosis and inflammation biomarkers (TNF-α, p=0.0006; IL-6, p=0.01; IL-1β, p=0.004) by regulating the fatty acid uptake (CD36, p<0.0001), synthesis (ACC1, p=0.003; FAS, p=0.02; DGAT, p=0.003; SREBP-1c, p=0.03; chREBP, p<0.0001), and oxidation (PPARα. p=0.01) marker. *Bifidobacterium* ameliorates NAFLD, dysbiosis, and gut microbiome metabolite through modu-

lation of gut microbiota resulting in reduced hepatic inflammation, steatosis, and fatty acid synthesis.

Conclusions: Our study highlighted the association between gut microbiota and NAFLD and the importance of the gut-liver axis and confirmed the potential of *Bifidobacterium* to improve NAFLD. Studying the mechanisms between probiotics and NAFLD will help design novel therapies.

Keywords: NAFLD, Gut-liver axis, Probiotics, Dysbiosis

FP-11

Landscape of T-Cell Exhaustion Heterogeneity in Hepatocellular Carcinoma: Insights from Integrating Whole Exome, Transcriptomes, and Single-Cell Sequencing

Soon Kyu Lee[1], Jinyeong Lim[2], Joo Yeon Jhun[3], Jong Young Choi[4], Ho Joong Choi[5], Young Kyoung You[5], Ji Won Han[4], Pil Soo Sung[4], Seung Kew Yoon[4], Mi-La Cho[3], Jeong Won Jang[4*]

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University, Seoul, Republic of Korea, [3]The Rheumatism Research Center, Catholic Research Institute of Medical Science, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [4]Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [5]Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

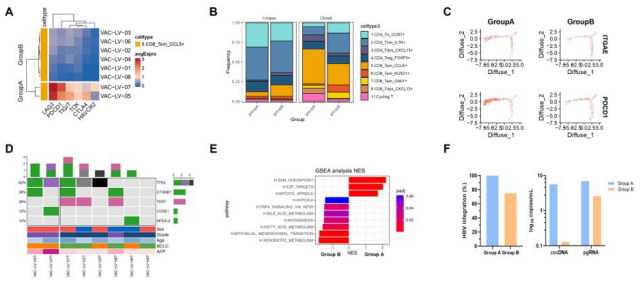
Aims: Immune checkpoint inhibitors have revolutionized treatment strategy in unresectable hepatocellular carcinoma (HCC) and have also been explored as an adjuvant therapy after surgery. Thus, investigating the heterogeneity of T-cell exhaustion in resected HCC is mandatory to improve the understanding of tumor microenvironment (TME) in HCC.

Methods: To delineate the heterogeneity of T-cell exhaustion and their developmental trajectoy, we performed single-cell RNA sequencing coupled with TCR sequencing analyses in HCC patients (n=8) who underwent liver resection. Moreover, whole exome sequencing (WES) and whole transcriptome sequencing were also integrated with the results of single-cell sequencing.

Results: We identified two distinctive patient groups based on the levels of $CD8^+$ T-cell exhaustion: high (n=2) or low (n=6), according to the expression scores of exhaustion markers including LAG3, PDCD1, TGIT, and CTLA4 (Figure 1A). We further revealed that the high exhaustion group showed higher clonal expansion in the $CCL5^+CD8^+$ T effector memory cells and cycling T cells with the higher expression of exhaustion genes than the low exhaustion group (Figure 1B). Results of trajectory analysis showed two distinct branches, one directed towards exhaustion and the other towards cytotoxic T cell lineages. The high exhaustion group was more likely to be directed towards the exhausted lineage, as evidenced by increased expression of $PDCD1^+$ or $TIGIT^+$ markers with clonal expansions (Figure 1C). The high exhaustion group also showed higher property of $CXCL13^+CD4^+$ T follicular hyper cells with the higher expression of PDCD1 compared to low exhaustion group. Moreover, higher expression of PDCD1 in the $FoxP3^+CD4^+$ regulatory T cells were also identified in the high exhaustion group. The high exhaustion group had the TP53 mutation identified by the WES analysis, while the low exhaustion group had mutations in the CTNNB1 and TERT promoter regions (Figure 1D). In WTS analysis, the high exhaustion group showed the activation of cell cycle related pathways, which might be associated with the increased proportion of HBV integration and level of cccDNA in the high exhaustion group (Figure 1E,F).

Conclusions: This study revealed the heterogeneity of T-cell exhaustion in the TME of resected HCC with verifying their differences in the gene expression and clonal expansion.

Keywords: Hepatocellular carcinoma, T cell, Tumor microenvironment, Exhaustion, PDCD1, Regulatroy T cell, Integration, TIGIT



FP-12

Analysis of Discordance between Transient Elastography and Liver Biopsy for Assessing Liver Fibrosis in Patients with Chronic Viral Hepatitis

Seong Hee Kang[1], Young Kul Jung[1], Tae Hyung Kim[2], Sun Young Yim[1], Young-Sun Lee[1], Yeon Seok Seo[1], Ji Hoon Kim[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Kwan Soo Byun[1]

[1]Department of Internal Medicine, Korea University College of Medicine, Korea, [2]Department of Internal Medicine, Hallym University College of Medicine, Korea

Aims: Vibration-controlled transient elastography (VCTE) is a non-invasive method used to assess liver fibrosis, which can be conveniently performed in an outpatient setting. However, discrepancies between VCTE results and biopsy findings are observed. The objective of this study was to determine the frequency of major discrepancies and identify the clinical variables associated with these differences.

Methods: Our institution established specific cutoff values for fibrosis assessment using VCTE: <7.5 kPa (F0-2) for mild to moderate fibrosis, ≥9.7 kPa (F3) for advanced fibrosis, and ≥14.9 kPa (F4) for cirrhosis. Liver fibrosis was evaluated using the METAVIR scoring system.

Results: We identified a total of 385 patients who underwent both VCTE and liver biopsy within one month. Among them, 130 patients had chronic hepatitis B, and 255 had chronic hepatitis C. The analysis revealed significant fibrosis (≥F2) in 303 patients (78.7%), advanced fibrosis (≥F3) in 195 patients (49.3%), and cirrhosis (F4) in 85 patients (22.1%). The area under the receiver operating characteristic curve (AUROC) values (95% confidence interval) for liver stiffness measurements to diagnose ≥F2, ≥F3, and F4 were 0.77 (0.71-0.83), 0.78 (0.74-0.83), and 0.75 (0.68-0.81), respectively. Among the patients,

209 (54.2%) exhibited discrepant results for the diagnosis of fibrosis. Of these, 83 patients (21.6%) had an overestimation of fibrosis by VCTE, while 126 patients (32.7%) had an underestimation. We found that high platelet counts, increased levels of aminotransferases, and particularly an elevation in ALT levels above 100 IU/L were associated with the overestimation of fibrosis. On the other hand, low levels of aminotransferases and bilirubin were associated with the underestimation of fibrosis.

Conclusions: Our findings demonstrate that overestimation or underestimation of fibrosis by VCTE is common, particularly in patients with high levels of clinical inflammatory activity. While VCTE is highly sensitive in detecting liver fibrosis, its specificity is not as reliable.

Keywords: Chronic hepatitis B, Chronic hepatitis C, Liver biopsy, Transient elastography

Oral Poster Presentation

Oral Poster Group 1. [NAFLD + Alcohol-Related Liver Disease]

OP-01

Solid Lipid Nanoparticle Ganodric Acid Ameliorates the High Fat Induced Non-Alcoholic Fatty Liver Disease via Alteration Gut Microbiota and PI3K/AKT/mTOR Signaling Pathway

D Chauhan[1], M Rahman[2], V Kumar[2]

[1]Department of Physics, Rajkamal Science & Management College, India, [2]Department of Pharmacy, SHIATS, India

Aims: Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by the accumulation of fat in the liver. NAFLD is considered a spectrum of liver conditions, ranging from simple fatty liver (steatosis) to a more severe form called nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and, in some cases, hepatocellular carcinoma (HCC), the most common type of primary liver cancer. Ganodric acid already showed the antioxidant and anti-inflammatory effect against various diseases. In this study, we fabricated the solid lipid nanoparticle (SLN) of ganodric acid (GA) and scrutinized the chemoprotective effect against high fat diet (HFD) and Diethylnitrosamine (DEN) induced NAFLD in rats.

Methods: Double emulsion solvent displacement model was used for the preparation of SLN-GA. Intraperitoneal administration of DEN (100 mg/kg) was used for the induction of HCC in rats for 2 weeks. The rats were divided into 2 groups and received the HFD with or without treatment with SLN-GA for 20 weeks. Body weight, tumor incidence, tumor nodules, hepatic, non-hepatic, apoptosis, antioxidant, pro-inflammatory and inflammatory were estimated. For the determination of gut microbiota, we collected the stools of all rats.

Results: Surface methodology showed the particle size (174.3 nm) and polydispersity index (0.228) for SLN-GA. SLN-GA remarkably suppressed tumor nodules (87.4%), tumor incidence (76.5%) and average size nodules (54.4%).SLN-GA remarkably decreased the level of AFP (76.4%), ALT (65.5%), AST (58.7%), ALP (61.7%), GGT (54.6%); non-hepatic parameters viz., bilirubin (53.5%), total protein (57.6%), respectively. SLN-GA also suppressed the level of SOD (47.6%), GSH (48.7%), GPx (53.4%), CAT (45.3%) and boosted the level of LPO (58.7%). SLN-GA significantly (p<0.001) suppressed the level of inflammatory cytokines like TNF-α (43.2%), IL-1β (49.1%), IL-6 (54.6%); inflammatory parameters such as COX-2 (54.3%), PGE2 (59.4%), VEGF (64.3%), iNOS (67.6%) and NF-κB (48.7%), respectively. SLN-GA significantly (p<0.001) altered the expression of Erbb2 (23.4%), Pik3rl (27.7%), PIk3ca (31.4%), Akt1 (32.5%) and Map3k1 (34.3%), respectively. Moreover, SLN-GA enhanced gut microbial richness and diversity and altered the relative abundance of *firmicutes* and *bactericides*, respectively.

Conclusions: SLN-GA remarkably suppressed the HFD-induced NAFLD in rats via alteration of gut microbiota and PI3K/AKT/mTOR Signaling pathway.

Keywords: Solid lipid nanoparticle, NAFLD, PI3K/AKT/mTOR Signaling pathway, Gut microbiota

OP-02

Inhibition of CHIT1 as a Potential Therapeutic Approach for Liver Fibrosis

Sung Woo Cho[1], Jung Hoon Cha[1], Na Ri PARK[1], Ji Won Han[1,2], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Pil Soo Sung[1,2], Si Hyun Bae[1,3]

[1]The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [3]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 03382, Republic of Korea

Aims: Macrophage activation and cytokine release play a pivotal role in liver fibrosis. The profibrotic macrophage is known to secrete human chitotriosidase (CHIT1). In this study, we focused on role of CHIT1 in liver fibrosis.

Methods: The concentration of CHIT1 in the sera of patients (n=62) with liver fibrosis was evaluated using ELISA. To investigate the effects of CHIT1 on liver fibrosis, TGF-b1 and recombinant human CHIT1 (rh-CHIT1) were treated on isolated human primary hepatic stellate cells Combination of Streptozocin (STZ) injection and feeding high fat and high cholesterol diet (HFHC) were used to establish liver fibrosis model.

Results: The level of CHIT1 was significant higher in patients with advanced fibrosis (F3 or F4) than in those with early fibrosis (F1 or F2) (p<0.01). In isolated human primary hepatic stellate cells, it was observed that the group treated with both TGF-b1 and rhCHIT1 showed enhanced TGF-b/SMAD signaling and an increase in alpha smooth muscle action (a-SMA) expression, a downstream target of TGF-b/SMAD signaling, compared to the group treated with TGF-b1 alone. In the STZ-HFHC mouse model, we identified the induction of liver fibrosis and increased expression of CHIT1 in macrophage phagocyte in the fibrotic liver by IHC and FACS. Treatment with OATD-01 resulted in an improvement in liver fibrosis in STZ-HFHC mice.

Conclusions: This study demonstrates the significant role of CHIT1 in liver fibrosis. Higher CHIT1 levels were observed in advanced fibrosis patients. *In vitro* experiments showed that combined TGF-b1 and rhCHIT1 treatment enhanced fibrotic signaling. In a mouse model, increased CHIT1 expression was found in fibrotic liver macrophages, and treatment with CHIT1 inhibitor OATD-01 improved fibrosis. Targeting CHIT1 holds therapeutic potential for liver fibrosis.

Keywords: Liver fibrosis, CHIT1, Macrophage activation, Therapeutic approach

OP-03

Prevalence and Predictors of Multidrug Resistant Bacteremia in Liver Cirrhosis

Aryoung Kim, Byeong Geun Song, Myung Ji Goh, Wonseok Kang, Dong Hyun Sinn, Geum-Youn Gwak, Yong-Han Paik, Moon Seok Choi, Joon Hyeok Lee

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Aims: As the prevalence of multiple drug-resistant (MDR) infections linked with higher motility in liver cirrhosis (LC) patients rises, it is crucial to understand the epidemiology and predicting factors of MDR bacteremia. MDR infection prevalence varies significantly across geographic locations. The goal of this study is to look at local epidemiology and antibiotic resistance patterns isolated from the bloodstream of LC patients in Korea, and to identify predictors of MDR bacteremia.

Methods: This retrospective study included 140 LC patients diagnosed with bacteremia between January 2017 and December 2022. The epidemiology and antibiotic resistance of these infections were studied, as well as the determinants of MDR bacteremia were analyzed using logistic regression analysis.

Results: The most frequently isolated bacteria in the bloodstream were *Escherichia coli* (E. coli) (n=45, 31.7%) and *Klebsiella spp.* (n=35, 24.6%). Thirty-four isolates (23.9%) were MDR, slightly lower prevalence than other geographic areas. Extended-spectrum beta-lactamase *Escherichia coli* (12.7%) and methicillin-resistant *Staphylococcus aureus* (4.5%) were the most commonly isolated MDR bacteria. When *Enterococcus* spp were cultured, the majority were MDR (MDR 83.3% vs. 16.7%, p=0.003), particularly vancomycin-susceptible *Enterococcus faecium*. Antibiotics administration within 30 days or/and nosocomial infection was a significant predictor of MDR bacteremia (OR: 4.31, 95% CI; 1.78-10.42, p=0.001). MDR bacteremia is not predicted by sepsis predictors such as positive of systemic inflammatory response syndrome (SIRS) (OR: 0.85, 95% CI; 0.33-2.24, p=0.75) or quick sequential organ failure assessment (qSOFA) (OR: 1.48, 95% CI; 0.67-3.23, p=0.33).

Conclusions: More than 70% of strains that can be treated with a third-generation cephalosporin have been cultured. In cirrhotic patients, antibiotic administration within 30 days or nosocomial infection was a predictor of MDR bacteremia; hence, broad-spectrum antibiotics should be given empirically if these risk factors exist.

Keywords: Multidrug resistant bacteremia, Liver cirrhosis, Epidemiology, Risk factor

OP-04

Dynamic Changes of Metabolic Dysfunction–Associated Fatty Liver Disease Status Were Associated with the Liver-Related Long-Term Outcomes: A Nationwide Cohort Study

Yun Mi Ko[1], Min Kyung Park[1], Hye-Sung Moon[2], Sung Won Chung[1], Sungho Won[2,3], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, [2]RexSoft Inc., Seoul 08826, Korea, [3]Department of Public Health Sciences, Graduate School of Public Health, Seoul National University, Seoul, South Korea.

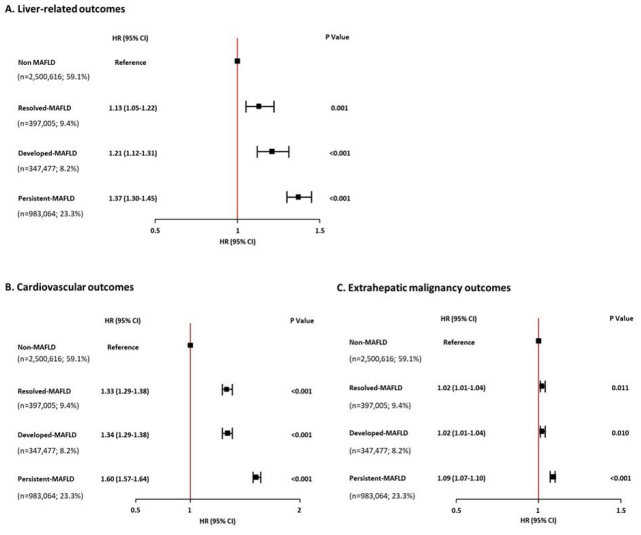
Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) status, defined by hepatic steatosis with metabolic dysfunction, could be dynamic changes by treatment such as lifestyle modification. We aimed to evaluate the association between the risk of MALFD long-term outcomes and changes in MAFLD status.

Methods: We analyzed data from 4,228,162 participants who participated in health screening programs both in 2009 and 2013 using nationwide claims data from the National Health Insurance Service of South Korea. Participants were divided into four groups based on changes in MAFLD status from 2009 to 2013; non-MAFLD, resolved-MAFLD, developed-MAFLD, and persistent-MAFLD. The primary outcome was the incidence of liver-related complications, and the secondary outcomes were the incidence of cardiovascular complications and primary extrahepatic malignancy.

Results: During the median follow-up of 6.4 years (interquartile range, 6.1–6.6 years), 7,828 patients (0.2%) were development liver-related complication. The persistent-MAFLD group had significant higher risk of liver-related complication compared to non-MAFLD group (adjusted hazard ratio [aHR]=1.37; 95% confidence interval [CI]=1.30–1.45; p<.001; Figure 1A), followed by the developed-MAFLD group (aHR=1.21; 95% CI=1.12–1.31; p<.001; Figure 1A) and resolved-MAFLD group (aHR=1.13; 95% CI=1.05–1.22; p<.001; Figure 1A). Interestingly, the recovered MAFLD group showed lower risk of liver-related outcomes compared to persistent MAFLD group (aHR=0.82; 95% CI=0.76–0.89; p<.001). The risk of cardiovascular complications and the risk of primary extrahepatic malignancy were also higher in the persistent-MAFLD than non-MAFLD group (aHR=1.60; 95% CI=1.57–1.64; p<.001; Figure 1B, aHR=1.09; 95% CI=1.07–1.10; p<.001; Figure 1C, respectively). On the sensitivity analysis after excluding underlying liver disease, the persistent MAFLD group maintained a significantly higher risk of liver-related complication than the non-MAFLD group (aHR=1.37; 95% CI=1.29–1.46; p<.001).

Conclusions: Patients with persistent MAFLD status showed a higher risk of liver-related complications than non-MAFLD patients. Patients with newly developed MAFLD also had a higher risk of liver-related complications than patients who never experienced the MAFLD, while resolved MAFLD status could ameliorate the risk of liver-related complications.

Keywords: MAFLD, Cardiovascular complications, Primary extrahepatic malignancy



OP-05

Polyethylene Glycol Reduces Hangover Symptoms with Protection of Liver and Intestine against Alcohol Consumption

Tom Ryu[1], Keungmo Yang[2], Byoung Young Choi[3], Won Gil Cho[3], Beom Sun Chung[3]

[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, [3]Department of Anatomy, Yonsei University Wonju College of Medicine, Wonju

Aims: Present study revealed the effectiveness of polyehtylene glycol (PEG) for hangover symptons with mouse model of binge drinking.

Methods: 8-week-old male C57BL6J wild type (WT) mice with vehicle, binge drinking (4 g/kg body weight), or binge drinking plus PEG (2 g/kg body weight) were analyzed by behavioral test and blood concentration test using gas chromatography. H&E, immunohistochemistry, and immunofluorescence staining were conducted with the slides of liver and intestine. Quantitative real-time polymerase chain reaction (qRT-PCR) and flow cytometry were utilized with tissue and mononuclear cells of liver and tissue of intestine.

Results: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and mRNA levels of *Cyp2e1* and *Tnf* were upregulated in binge drinking group of mice, compared to controls. Elevated neutrophil iniiltration and increased damage of hepatocytes were observed by flow cytometry and histologic finding in binge drinking grooup. Also, collpased intestinal barrier and activated cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase (ADH) were shown in slides of intestine in acute alcohol comsuption group, compared to the vehicle. Concentrations of ethanol and acetadehyde in blood were increased and behavioral test showed impaired motor function of mice in the binge group. Interestingly, PEG administration after alcohol consumption significantly downregulated serum AST and ALT levels and decreased mRNA level of *Tnf* of liver tissue. Liver injury was recovered and neutrophil infiltration was decreased with liver of additional PEG-treated mice. Morever, gut injury was reduced and expression of ADH and CYP2E1 in the gut barrier were downregulated in histologic findings of intestine of PEG group. Increased blood concentration of ethanol and acetaldehyde and motor impairment due to acute ethanol consumption drastically recovrered with PEG administration.

Conclusions: PEG administration after acute binge drinking would be a novel therapeutic option for protection of liver and gut, and reducing hangover symptoms.

Keywords: Polyethylene glycol, Alcoholic liver disease, Intestine, Hangover

OP-06

Proposal of a Novel Serological Algorithm Combining FIB-4 and Serum M2BPGi for Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease

Dong Hyun Kim[1], Yeo Wool Kang[1], Sang Yi Moon[1], Yang Hyun Baek[1], Se Young Jang[2], Dae Won Jun[3,4], Ki Tae Yoon[5,6], Young Youn Cho[7], Hoon Gil Jo[8], Ae jeong Jo[9]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea, [2]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Korea, [3]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea, [4]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, Korea, [5]Department of Internal Medicine, College of Medicine, Pusan National University, Busan, Korea, [6]Liver Center, Pusan National University Yangsan Hospital, Yangsan, Korea, [7]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea, [8]Division of Gastroenterology, Department of Internal Medicine, Wonkwang University College of Medicine and Hospital, Iksan, Korea, [9]Department of Information Statistics, Andong National University, Andong, Korea

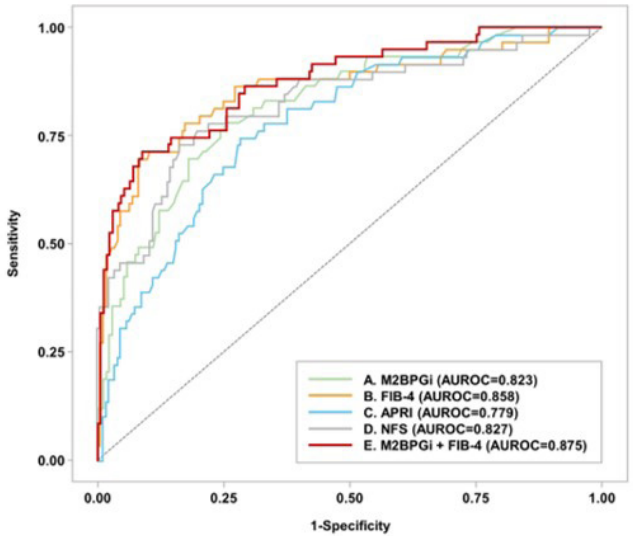
Aims: Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of chronic liver disease worldwide. It can progress to liver cirrhosis and hepatocellular carcinoma. Although liver biopsy is the gold standard for evaluating liver fibrosis in NAFLD, it has several clinical limitations, including invasiveness, sampling error, relative high cost, and variations of histologic interpretations. Therefore, algorithm using non-invasive test has been proposed to exclude advanced fibrosis in order to avoid unnecessary liver biopsy. Serum Mac-2 binding protein glycosylation isomer (M2BPGi) is a non-invasive marker for liver fibrosis and it can provide results from a single blood sample. We evaluate whether advanced fibrosis can be further excluded through two steps using FI4 and M2BPGi in NAFLD.

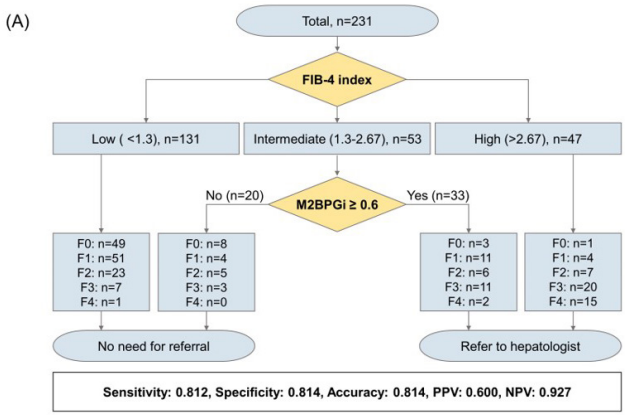
Methods: From March 2015 to September 2022, we enrolled 231 patients diagnosed with NAFLD at Dong-A University Hospital and Kyungpook National University Hospital who underwent liver biopsy in this retrospective study. Liver fibrosis stage was assessed according to the system devised by the nonalcoholic steatohepatitis (NASH) clinical research network (CRN) scoring system. F3-F4 was defined as an advanced fibrosis. As a non-invasive method for assessing liver fibrosis, serum M2BPGi, fibrosis index based on four factors (FIB-4), and non-alcoholic fatty liver disease fibrosis score (NFS) were evaluated. The accuracy of non-invasive markers in the diagnosis of liver fibrosis was calculated using area under the receiver–operator curve (AUROC) analysis. Statistical significance was considered at *P*-value <0.05.

Results: The average age of enrolled patients was 45.7 years. There were 124 (53.7%) males. Associated metabolic diseases were obesity (body mass index ≥ 25 kg/m^2) (n=195, 84.4%) and diabetes (n=75, 32.5%). The confirmed fibrosis grade in liver biopsy was F0 in 61 (26.4%) patients, F1 in 70 (30.3%), F2 in 41 (17.8%), F3 in 41 (17.8%), and F4 in 18 (7.8%). AUROCs of serum M2BPGi, FIB-4, and NFS for advanced fibrosis were 0.823, 0.858, and 0.827, respectively (Fig. 1). To reduce the performance of unnecessary liver biopsy, we propose a two-step algorithm using FIB-4 as an initial diagnostic tool and serum M2BPGi (≥0.6) as an additional diagnostic method for patients classified as intermediate (23%) (Fig. 2). Using the proposed algorithm, the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were 0.812, 0.814, 0.814, 0.600, and 0.927, respectively.

Conclusions: Serum M2BPGi is a simple and effective test for advanced fibrosis in patients with NAFLD. Application of the two-step algorithm based on FIB-4 and M2BPGi proposed here can improve diagnostic performance and reduce unnecessary tests, making diagnosis easily accessible, especially in primary medical centers.

Keywords: Non-alcoholic fatty liver disease, Mac-2 binding protein glycosylation isomer, Advanced fibrosis





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OP-07

Prognosis after Sustained Virologic Response of Chronic Hepatitis C Patients Treated with Sofosbuvir Based Treatment: 5 Years Follow up Data of Multicenter Prospective Observational Study

Jeong Han Kim[1], Jae Hyun Yoon[2], Yohan Lee[2], Sung Eun Kim[3], Ji Won Park[3], Gi-Ae Kim[4], Yewan Park[4], Seong Hee Kang[5], Yoonseok Lee[6], Young-Sun Lee[6]

[1]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Chonnam National University Hospital School of Medicine, Gwangju, Korea, [3]Department of Internal Medicine, Hallym University College of Medicine, Anyang, Korea, [4]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea, [5]Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea, [6]Department of Internal Medicine, Korea University Medical Center, Seoul, Korea

Aims: Direct-acting antiviral (DAA) therapy can cure chronic hepatitis C (CHC) and sofosbuvir (SOF) and ledipasvir (LDV)/SOF were introduced to Korea in 2016. A good prognosis is expected in patients who achieved sustained virologic response (SVR) after DAA treatment. However, information about the prognosis of Korean CHC patients who achieved SVR after SOF-based treatment is still limited. We aimed to investigate the prognosis of these patients.

Methods: This is a multicenter prospective observational study. The CHC patients achieved SVR after SOF or LDV/SOF treatment were enrolled and the final follow-up date was December 2022. The primary end-point was hepatocellular carcinoma (HCC) occurrence and the secondary end-points was recurrence or reinfection. At last one time in a year, we checked about this end-point.

Results: A total of 509 patients was included in this analysis and the mean follow-up duration was 37.0 months. The male 229 patients (45.0%) and the mean age was 61.9 years. Genotypes were 1 (91, 17.9%), 2 (416, 81.7%), and 3 (2, 0.4%). SOF and ribavirin combination was the most common treatment (391, 76.8%). Cirrhosis was 159 patients (31.2%) and the mean Child-Pugh score was 5.1. HCC occurrence cases were 16 patients (3.1%) for up to 5 years. HCC patients had more cirrhosis prevalence (81.3% vs. 29.6%, $p<0.001$), higher alpha-fetoprotein level (6.0 vs. 3.3, $p=0.020$), and higher FIB-4 (5.6 vs. 2.6, $p=0.001$). Cox regression analysis showed cirrhosis ($p=0.046$) was a significant risk factor for HCC occurrence. Recurrence or reinfection occurred in 2 patients (0.4%) 18 and 31 months after SVR each.

Conclusions: The prognosis of patients who achieved SVR after SOF based treatment was generally good. However, HCC risk was not wholly removed especially in cirrhosis patients. Recurrence or reinfection is also possible. Therefore, regular follow-up surveillance is still warranted and early treatment is essential.

Keywords: Hepatitis C, Direct-acting antiviral, Sustained virologic response, Sofosbuvir

OP-08

Increased Risk of Osteoporotic Fractures in Patients with Primary Biliary Cholangitis

Jihye Lim[1], Ye-Jee Kim[2], Sehee Kim[2], Jonggi Choi[3]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

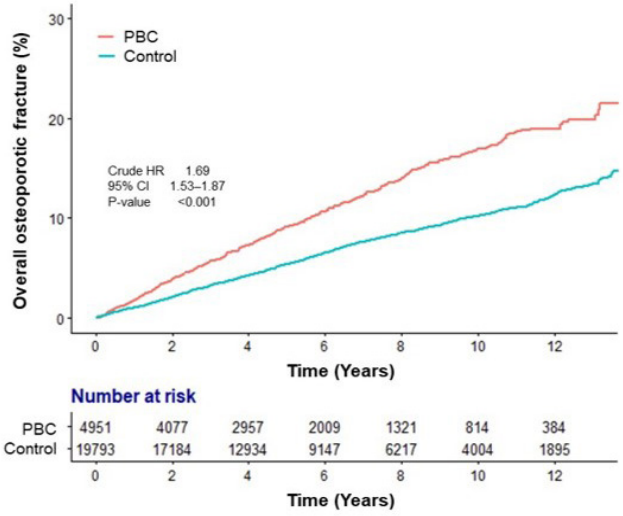
Aims: Large-scale studies on the risk of osteoporotic fractures in patients with primary biliary cholangitis (PBC) are limited due to low incidence. We aimed to investigate whether PBC is associated with osteoporotic fractures using real-world nationwide data.

Methods: The Korean National Health Insurance Service claims data from 2007 to 2020 were analyzed in this population-based cohort study. Patients with PBC (n=4,951) were matched with controls (n=19,793) using a 1:4 ratio based on age, sex, and follow-up duration. The primary outcome was osteoporotic fracture, which comprised fractures of the vertebra, hip, distal radius, and proximal humerus.

The incidence rates (IRs) and hazard ratios (HRs) were determined to assess the impact of PBC on osteoporotic fractures.

Results: During the median follow-up period of 5.37 years, 524 patients in the PBC group had osteoporotic fractures (IR, 18.59/1,000 person-years [PYs]). After adjusting for covariates, PBC increased the risk of osteoporotic fractures by 1.63-fold (95% confidence interval, 1.20–2.22; p=0.002). The vertebra and hip were particularly susceptible to fracture in patients with PBC, with adjusted HRs of 1.77 and 2.23, respectively. In the subgroup analysis, the risk of osteoporotic fracture was 2.53-fold higher in men and 1.59-fold higher in women with PBC than that in the respective matched control groups.

Conclusions: Patients with PBC had a higher risk of osteoporotic fractures than their matched controls. Considering the morbidity and mortality related to osteoporotic fractures, increasing awareness of osteoporotic fracture risk and implementing appropriate preventive measures in patients with PBC are imperative.



Keywords: Cholestasis, Hepatic osteodystrophy, osteoporosis

OP-09

Azathioprine on Risk of Extrahepatic Malignancy in Patients with Autoimmune Hepatitis: A Nationwide Claims Study in South Korea

Sung Hwan Yoo[1], Hyun Woong Lee*[1], Jung Il Lee[1], Gi Hyeon Seo[2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Korea, [2]Health Insurance Review and Assessment Service, Seoul, South Korea

Aims: Long-term immunosuppressive therapy in patients with autoimmune hepatitis (AIH) increases the risk of extrahepatic malignancy in addition to hepatocellular carcinoma. However, the risk of extrahepatic malignancy is unknown in Korean AIH patients. We aimed to evaluate the impact of azathioprine (AZT) treatment on extrahepatic malignancy risks.

Methods: We identified all persons diagnosed with AIH between 2008 and 2020. We included 8,280 patients with AIH, using the national claims data of the Health Insurance Review and Assessment Service (HIRA). The numbers of patients treated with and without AZT were 3,059 and 5,221, respectively. We estimated the cumulative risks of extrahepatic malignancy and hazard ratios (HRs) between patients treated with and without AZT.

Table 1. **Characteristics of patients and controls**

		Total N = 8,280		Patient N = 3,059		Control N = 5,221		P-value
Age		56.7+13.5		57.2+12.6		56.5+14.0		0.011
	18-64	5,811	70.2%	2,150	70.3%	3,661	70.1%	0.881
	65-90	2,469	29.8%	909	29.7%	1,560	29.9%	
Sex	male	1,299	15.7%	483	15.8%	816	15.6%	0.851
	female	6,981	84.3%	2,576	84.2%	4,405	84.4%	
Comorbidity	DM	2,418	29.2%	957	31.3%	1,461	28.0%	0.001
	LC	3,131	37.8%	1,102	36.0%	2,029	38.9%	0.010
Steroid		4,180	50.5%	2,614	85.5%	1,566	30.0%	<0.001
Follow-up	(month)	49.8+43.1		28.8+27.6		62.1+45.8		<0.001

Table 2. **Cancer risks for patients with AZT and without AZT in AIH**

		Total N = 8,280	Patient N = 3,059	Control N = 5,221	P-value
All cancer	cancer	433	100	333	
	person-year	34,381	7,349	27,032	
	Incidence(/100 py)	1.26(1.14-1.38)	1.36(1.11-1.65)	1.23(1.10-1.37)	
	crude HR		1.08(0.86-1.36)	ref	0.530
	adj HR		1.14(0.87-1.49)	ref	0.347
HCC	cancer	139	33	106	
	incidence(/100 py)	0.40(0.34-0.48)	0.45(0.31-0.63)	0.39(0.32-0.47)	
	crude HR		1.11(0.74-1.66)	ref	0.603
	adj HR		1.25(0.78-2.01)	ref	0.351
Non-HCC	cancer	294	67	227	
	incidence(/100 py)	1.26(1.14-1.38)	1.36(1.11-1.65)	1.23(1.10-1.37)	
	crude HR		1.06(0.80-1.40)	ref	0.685
	adj HR		1.09(0.79-1.51)	ref	0.600

Results: Among 8,280 patients, the mean age was 56.7±13.5 years, 84.3% were women, and the follow-up period was 49.8±43.1 months. The mean age and sex are not different between patients treated with and without AZT. However, the number of patients with diabetes was higher in patients treated with AZT (31.3% vs. 28.0%). The number of patients with liver cirrhosis was higher in patients treated without AZT (36.0% vs. 38.9%). At the time of diagnosis, 85.5% of patients with AZT and 30.0% of patients without AZT were treated with steroids for more than 90 days (p<0.001). The incidence of extrahepatic malignancy was 1.36 and 1.23 per 100 person-years in the patients treated with AZT and without AZT, respectively (p=0.685). After we adjusted for confounding by age, sex, diabetes, and liver cirrhosis, the HR was 1.09 (95% confidence interval 0.79–1.51, p=0.600).

Conclusions: The national claims data of HIRA did not show that AZT significantly increases the risk of extrahepatic malignancy among AIH patients.

Keywords: Autoimmune hepatitis, Azathioprine, Extrahepatic malignancy

OP-10

Mathematical Modeling to Evaluate Feasibility and Strategies for Controlling Hepatitis B Virus Infection in Indonesia

Prihantini[1], Rifaldy Fajar[2], Hannah Moa Jimenz[3], Asfirani Umar[4]

[1]Department of Mathematics, Bandung Institute of Technology, Indonesia, [2]Department of Mathematics and Computer Science, Karlstad University, Sweden, [3]Department of Public Health, Karlstad University, Sweden, [4]Department of Mathematics, Hasanuddin University, Indonesia

Aims: Hepatitis B virus (HBV) infection remains a significant public health burden in Indonesia, necessitating urgent interventions to reduce its impact. The World Health Organization (WHO) has set a challenging target of achieving a prevalence of just 0.1% of HBV surface antigen (HBsAg) among children in Indonesia by 2030, aiming to eliminate viral hepatitis as a substantial public health threat. However, the feasibility of attaining this target and the necessary strategies in Indonesia remain uncertain, despite notable progress made in hepatitis B control. This study aims to assess the feasibility of reaching the WHO's 0.1% HBsAg prevalence target among children in Indonesia by 2030 and identify critical developments required to meet this goal.

Methods: A dynamic compartmental model was developed, incorporating age and time, to capture the complex dynamics of HBV infection and reflect the current state of hepatitis B control in Indonesia. Extensive simulations were conducted from 2006 to 2050, considering three scenarios: maintaining the current interventions (status quo), integrating peripartum antiviral prophylaxis (PAP) with current interventions, and scaling up existing interventions while implementing PAP.

Results: The prevailing situation showcased a gradual decline in HBsAg prevalence across various age groups. However, achieving the WHO's ambitious target of 0.1% prevalence among children under 5 years was estimated to be attainable by 2037. These findings were reaffirmed through rigorous sensitivity analyses, highlighting the reliability of the projections. Notably, the introduction of peripartum antiviral prophylaxis (PAP) in conjunction with current interventions resulted in a notable reduction in HBsAg prevalence among children under 5 years. This decline was even more pronounced when accompanied by a higher successful interruption coverage achieved through PAP implementation. Nevertheless, it's important to recognize that even with a 90% success rate by 2030, the target of 0.1% prevalence would not be met until 2031. However, by scaling up the existing interventions, integrating PAP, and simultaneously expanding its scope, Indonesia could potentially achieve the WHO's target either on schedule or even one year earlier. This outcome is contingent upon the timely introduction of PAP and the scaling up of successful interruption coverage to either 80% or 90% by 2030, respectively.

Conclusions: The achievement of the WHO's target of 0.1% HBsAg prevalence among children in Indonesia by 2030 presents a formidable challenge with the current interventions. The implementation of PAP could serve as a crucial strategy in expediting the attainment of this target. A comprehensive scale-up of available interventions, including the introduction of PAP, is vital to ensure Indonesia's success. These findings emphasize the urgent need for targeted strategies and sustained efforts to eliminate viral hepatitis as a substantial public health threat in Indonesia, ultimately striving to meet the WHO's target by 2030 or even earlier.

Keywords: Mathematical modeling, Hepatitis B virus, Feasibility, Strategies

OP-11

Intrahepatic IgA Complex Induces Polarization of CAFs into Matrix CAFs and Upregulates PD-L1 Expression in the Tumor Microenvironment of HCC

Jong Geun Park[1], Pu Reun Roh[1], Min Woo Kang[1], Ji Won Han[1,2], Jeong Won Jang[1,2], Si Hyun Bae[1,3],Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jae Yong Ryu[4], Pil Soo Sung,[1,2]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]Division of gastroenterology and hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 03382, Republic of Korea, [4]Department of Biotechnology, Duksung Women's University, 33 Samyang-ro 144-gil, Dobong-gu, Seoul 01369, Korea

Aims: Cancer associated fibroblasts (CAFs) are a group of activated fibroblasts and play a key role in the tumor microenvironment (TME). Immunoglobulin A (IgA) usually neutralizes pathogens against infections at the mucosal sites. IgA has also been reported to contribute to inflammation or dismantling antitumor immunity in human liver. we investigated the effects of IgA complex on CAFs in TME of HCC.

Methods: The dynamics of CAFs in the TME of HCC were analyzed using single-cell RNA sequencing in three HCC samples. CAFs were isolated from thirty HCC samples. Isolated CAFs were treated with mock or serum-derived IgA dimer. CD71 and PD-L1 expression levels in CAFs were analyzed by flow cytometry. After treated with mock or IgA *in vitro*, co-culture experiment performed using CAF & CD8 + T cell.

Results: We identified five CAF subtypes in the TME of HCC. In a patient with high IgA serum, the sub-cluster proportions in matrix CAF-FAP were significantly increased. We performed flow cytometry on fresh surgical tissues and observed a significant increase in the MFI of FAP(p=0.001) in CD68+ cells from patients with high serum IgA(n=14) compared to those with low serum IgA(n=8). Furthermore, we observed a significant increase in the MFI values of CD71 and PD-L1(p<0.05) in the matrix CAF-FAP from patients with high IgA serum compared to those with low IgA serum. We have confirmed that the transferrin receptor (CD71) is expressed in CAFs. IgA -treated CAFs showed increased PD-L1 MFI values compared with mock-treated CAF. CD8 + T cells co-cultured with IgA -treated CAF showed decreased TNF-α MFI values compared with CD8 + T cells co-cultured with mock-treated CAF.

Conclusions: The correlation between IgA cpmplex and matrix CAFs may contribute to the establishment of immunosuppressive TME and poor prognosis of patients. Targeting this CAF subtypes may overcome the resistance of Immune checkpoint blockade therapy.

Keywords: Hepatocellular carcinoma, Cancer associated fibroblast, Immunoglobulin A

OP-12

Role of Portosystemic Shunt and Portal Vein Stent in Managing Portal Hypertension due to Hematological Malignancies

Ji Hoon Kim[1], Suho Kim[2], Ji Won Han[1], Jeong Won Jang[1], Jong Young Choi[1], Seung Kew Yoon[1], Ho-Jong Chun[2], Jung-suk Oh[2], Sung-Eun Lee[3], Pil Soo Sung[1]

[1]Department of Gastroenterology and Hepatology, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [2]Department of Radiology, Seoul St mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [3]Department of Hematology, Seoul St mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Aims: A considerable number of patients with hematological malignancies experience complications related to portal hypertension. Many of these patients experience many complications of portal hypertension, including life-threatening complications such as varix bleeding. In our study, we sought to analyze the prognosis of patients of hematological malignancies with portal hypertension treated with transjugular intrahepatic portosystemic shunt and portal vein stents.

Methods: We retrospectively assessed patients with hematological malignancies with portal hypertension who had complications including varix bleeding and ascites. We evaluated the prognosis of enrolled patients who were treated with portal vein stents and transjugular intrahepatic portosystemic shunts and also evaluated factors that seemed to be associated with their prognosis.

Results: A total 11 patients with hematological malignancies who experienced TIPS or portal vein stent were evaluated. 4 patients were myelodysplastic syndrome patients; 3 patients were primary myelofibrosis (all positive for JAK2 V617F mutation) patients; 2 patients were multiple myeloma patients; 1 patient was essential thrombocytosis patient. The median follow-up duration was 420 days. 3 patients had portal vein thrombosis. The median total bilirubin of the 11 patients was 2.73 and the median INR of the patients was 1.17. None of the patients tested positive for HBV or HCV infection. Of the 11 patients, 8 patients showed resolution of portal hypertension and complications following TIPS and stent insertion. 1 patient experienced rebleeding. 2 patients also experienced rebleeding but this was because they went through TIPS closure or revision due to repetitive hepatic encephalopathy.

Conclusions: Portosystemic shunt and stent installation is an effective treatment option in managing portal hypertension due to hematological diseases.

Keywords: Portal hypertension, TIPS, Portal vein stent, Hematological malignancy

Table 1. Baseline characteristics of enrolled patients

	Total (n=11)
Sex (M/F)	2(18%)/9(82%)
Age	53.64±9.82
Etiology	
Primary myelofibrosis	3 (27.27%)
JAK2 V617F mutation	(3)
Myelodysplastic Syndrome	3(27.27%)
Multiple myeloma	2(18.18%)
Essential thrombocytosis	1(9.09%)
Aplastic anemia	1(9.09%)
Polycythemia Vera	1(9.09%)
HBsAg	0
Anti-HCV Ab	0
Portal vein thrombosis	4(36.36%)
Treatment	
Eculizumab	2(18.18%)
Ruxolitinib	1(9.09%)
History of BMT	1(9.09%)
No history of chemotherapy or BMT	7(63.63%)

Table 2. Prognosis and changes in liver function of enrolled patients

	Total (n=11)
Initial lab	
Median total bilirubin (mg/dL)	0.88
Median albumin (g/dL)	3.7
Median INR	1.17
Last lab	
Median total bilirubin (mg/dL)	0.63
Median albumin (g/dL)	3.6
Median INR	1.14
Deaths	5
Portal hypertension related mortality	2
Rebleeding or aggravation	3

Oral Poster Group 3. [Viral Hepatitis]

OP-13

Comparison of the Effects of Switching from Tenofovir Disoproxil Fumarate to Either Entecavir or Tenofovir Alafenamide on Kidney Function in Chronic Hepatitis B: Retrospective Cohort Study

Eunjee Lim, Jihye Kim, Gwang Hyeon Choi, Eun Sun Jang, Sook-Hyang Jeong, Jin-Wook Kim

Department of Medicine, Seoul National University Bundang Hospital

Aims: Prolonged use of nucleos(t)ide analogues (NAs) such as ade-

fovir or tenofovir disoproxil fumarate (TDF) may negatively impact kidney function in individuals with chronic hepatitis B (CHB). Entecavir (ETV) and tenofovir alafenamide (TAF) are considered less nephrotoxic than adefovir or TDF, but it is not clear whether there is difference in the renal effects between ETV and TAF. Therefore, we investigated the effect of switching from TDF to either TAF or ETV on estimated glomerular filtration rate (eGFR) and creatinine (Cr) in chronic hepatitis B patients.

Methods: This retrospective study evaluated 172 patients with CHB who had been treated with TDF and switched to either ETV (n=59) or TAF (n=113). The reference dates were set to the end date of TDF intake. Patients were excluded if ETV or TAF administration period was less than 6 months after the end of TDF intake. The serial changes of creatinine and eGFR between the two groups were compared using a t-test analysis.

Results: The serial change in mean creatinine levels were higher in ETV group compared to TDF intake (0.22 mg/dL and -0.02 mg/dL, respectively, p=0.03). The mean decrease in eGFR was also significantly larger in ETV compared to TAF(-5.26 vs. -0.14 ml/min/1.73 m2, p=0.04). There was no significant difference observed in ALT levels (-42.24 vs -27.86 IU/L, p=0.57) and HBV DNA levels (-11400000 vs -4180972, p=0.06) between the two reference dates.

Conclusions: We found that renal function was better preserved in patients who receive TAF compared to ETV following the switch from TDF. Further research is required to compare the long-term effect of ETV and TAF on kidney function.

Keywords: Hepatitis B, ETV, TAF, TDF

OP-14

Prevalence of Hepatitis B Virus Core Antibody in Indian Blood Donors: Implications for Safe Transfusion

Ashok Kumar Sah[1], Pramod Kumar Sharma[1], Sparsh Kunwar[2], Kajal Arora[1]

[1]School of Medical & Allied Sciences, Galgotia University, Greater Noida, UP, India, [2]Department of Pulmonary Medicine, SGPGI, Lucknow, UP, India

Aims: This study evaluated replacement donors' anti-HBc testing status and risk variables for anti-HBc positivity among donors with Occult HBV infection (OBI).

Methods: Blood samples taken from blood donors between September 2021 and December 2021 were used in the study, which was carried out at the University Hospital Blood Bank in New Delhi, India. HBV DNA was identified using a semi-nested polymerase chain reaction, and donors were tested for HBsAg using a rapid diagnostic test (RDT), enzyme-linked immunosorbent assay (ELISA), and anti-HBc by ELISA.

Results: Out of the 275 subjects, 15 (5.5%) tested positive for HBsAg by RDT, 36 (13.1%) by ELISA, and 133 (48.5%) tested positive for anti-HBc. 107 (46.1%) of the 232 donors who tested negative for HBsAg were anti-HBc positive. Only one (0.93%) of the 107 samples with anti-HBc positivity but no HBsAg was HBV DNA positive. The donor tested positive for HBV DNA but tested negative for HBsAg by both RDT and ELISA.

Conclusions: Through this investigation, a possible danger of HBV transmission from isolated anti-HBc-positive donors to blood recipients has been established. It is possible to stop the spread of HBV through blood transfusions by using HBc immunoglobulin (antibody) M testing to select blood units that need to undergo additional testing using a polymerase chain reaction to look for OBI.

Keywords: Donors, Anti-HBc antibodies, Safe transfusion, Occult HBV

OP-15

In Silico and in Vitro Anti-Hepatitis B Virus Activity of Bioassay-Guided Compound Quercetin and Myricetin-3-O-Rhamnoside from Pistacia Lentiscus

Niti Singh[1], D. Singh[2], M.Singh[3]

[1]MarLabs Innovation PVt LTD, [2]SHUATS, [3]HMFA-MIET, India

Aims: Acute and chronic hepatitis B are disorders of the liver brought on by the hepatitis B virus (HBV). The current study describes the column-guided isolation and structural characterization of two anti-HBV compounds from *Pistacia lentiscus* utilizing an HBV-reporter cell culture paradigm, as well as the molecular docking elucidation of the mode of action.

Methods: *Pistacia lentiscus* leaves recently demonstrated *in vitro* anti-hepatitis B virus (HBV) action, and quercetin and other flavonoids were identified by HPTLC. Here, we describe the bioassay-directed fractionation of *Pistacia lentiscus* leaves using column chromatography and the isolation of two flavonoinds from the n-butanol fraction, as well as the determination of their structures (1H, 13C, and 2D-NMR) and evaluation of their antiviral activities (HBsAg and HBeAg assay) in HBV-reporter HepG2.2.2.15 cells.

Results: The HBV polymerase (Pol/RT) and capsid (Core) proteins, as well as the host-receptor sodium taurocholate co-transporting polypeptide (NTCP), were subjected to further molecular docking. Myricetin-3-O-rhamnoside and quercetin were recognized as the two isolated bioactive substances that are to be isolated from *Pistacia lentiscus*. In comparison to myricetin-3-O-rhamnoside, quercetin considerably decreased the synthesis of HBsAg and HBeAg by 43% and 36%, respectively, and by roughly 58% and 64%, respectively. The two anti-HBV flavonoids' greater affinity for Pol/RT than NTCP and Core was revealed by molecular docking.

Conclusions: By binding to viral Pol/RT and Core as well as host NTCP proteins, their potential route of anti-HBV activity is indicated. And shown that both chemical compounds isolated from *Pistacia lentiscus* were found to be effective and suggested potential virus inactivation mechanisms

Keywords: Hepatitis, Leaves, Molecular docking, Cell lines

OP-16

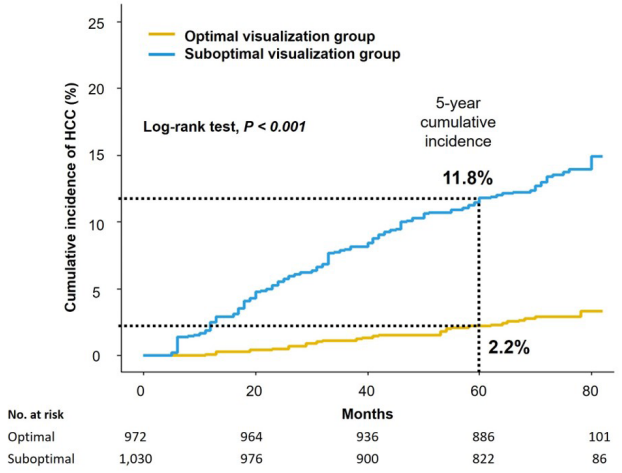
The Effectiveness of Ultrasonography-Based Surveillance of Hepatocellular Carcinoma according to the Ultrasound LI-RADS Visualization Score in Chronic Hepatitis B Patients

Yun Mi Ko[1], Min Kyung Park[1], Dong Ho Lee[2], Bo Yun Hur[3], Hyung-Chul Lee[4], Yun Bin Lee[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Radiology, Seoul National University College of Medicine, Seoul, Korea, [3]Department of Radiology, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Korea, [4]Department of Department of Anesthesiology, Seoul National University College of Medicine, Seoul, Korea

Aims: Ultrasonography (US) is a standard surveillance tool of hepatocellular carcinoma (HCC) in high-risk groups. However, the effectiveness of US-based surveillance of HCC would vary among the different individuals. This study evaluated the detection power of US and the occurrence of HCC according to the US Liver Imaging Reporting and Data System (LI-RADS) visualization score in chronic hepatitis B (CHB) patients.

Methods: Consecutive patients with CHB undergoing regular HCC surveillance were included in this retrospective cohort study. Outcomes of interest included cumulative incidence of HCC and false-negative rate of US in the optimal (LI-RADS visualization A) vs. suboptimal visualization groups (visualization B/C).



Results: A total of 2,002 patients were included in this study: 972 and 1,030 in the optimal and suboptimal visualization groups, respectively. Causes of suboptimal visualization included parenchymal heterogeneity from advanced cirrhosis (n=489), limited penetration from fatty liver (n=200), and limited window from overlying organ shadow (n=341). During a median follow-up of 75 months (interquartile range=69–77 months), 163 patients developed HCC. Compared to the optimal visualization group, the suboptimal visualization group had significantly higher risk of HCC (2.38%/yr vs. 0.48%/yr: hazard ratio=4.93, 95% confidence interval [CI]=3.28–7.41, p<0.001, Figure 1) and higher false-negative rate of US (43.9% vs. 16.7%: odds ratio=3.90, 95% CI=1.02–15.00, p=0.04). On sensitivity analysis with a subgroup excluding cirrhotic patients, the suboptimal visualization group maintained a significantly higher HCC risk than those in the optimal visualization group (0.61%/yr vs. 0.20%/yr; hazard ratio=3.09, 95% CI=1.36–6.99, p=0.004).

Conclusions: Among CHB patients, the suboptimal visualization group had a higher risk of both HCC development and false-negative rates of US. Surveillance using alternative computed tomography or magnetic resonance imaging might be highly recommended for CHB patients with US LI-RADS visualization B or C.

Keywords: LI-RADS, HCC, Chronic hepatitis B, Surveillance

OP-17

Effectiveness of Phyllanthus Urinaria Leaves Combined with Tenofovir in Treatment of Chronic Hepatitis B

Ha Linh[1], Nguyen Khac Hung Manh[2], Le Quoc Tuan[1]

[1]103 Cam Khe Clinic, [2]Thai Nguyen University of Medicine and Pharmacy, Vietnam

Aims: Aims: Evaluating the effectiveness of Phyllanthus urinaria (PU) combined with Tenofovir disoproxil fumarate (TDF) in the treatment of chronic hepatitis B

Methods: Study on a randomized controlled clinical trial in HBeAg (+) chronic hepatitis B patients from August 2018 to December 2022. One group received TDF 300 mg, the other group received TDF 300 mg combined with PU 800 mg.

Results: The percentages of ALT ≤ 40 UI/L after 6, 12, 18 months of PU-TDF group were 82%, 95%, 98% respectively, in comparison to the TDF group with the rates 51%, 75%, 90%, respectively. The percentages of AST ≤ 40 UI/L after 6, 12, 18 months of PU-TDF group were 81%, 94%, 96%, respectively, higher than the TDF group with the rates 68%, 87%, 90% (p<0.05).

Early response of HBV DNA after 6 months with HBV DNA reduction rate >1 log copies/mL and >2 log copies/mL in the PU -TDF group were 81%, 66% respectively, which are higher than in the TDF group with the rates of 71% and 52%. The rates of response to reduce HBV DNA below the detection threshold (<250 copies/ml) in the PU-TDF group after 6, 12, 18 months were 22%, 78%, 98% respectively, which are higher than TDF group with the rates11%, 61%, 87% (p<0.05).

The rate of the seroconversion from HBeAg (+) to HBeAg (-) in the PU-TDF group after 6, 12, 18 months were 6%, 18%, 36%, respectively, higher than those in the TDF group with the rates of 2%, 9%, 22% (p<0.05) respectively. The rate of HBeAg (-) and anti HBe (+) in the PU-TDF group after 6,12, 18 months were 5%, 14%, 19% which are higher than those in TDF group with the rates of 1%, 4%, 9% (p<0.05).

Conclusions: The combination of PU and TDF is more effective than TDF alone in the treatment of chronic hepatitis B.

Keywords: Chronic hepatitis B, Phyllanthus urinaria (PU), Tenofovir disoproxil fumarate (TDF), Treatment, Effective

OP-18

Association between Baseline Viral Load and On-Treatment Risk of Hepatocellular Carcinoma in Chronic Hepatitis B

Won-Mook Choi,[1] Gi-Ae Kim,[2] Jonggi Choi,[1] Gwang Hyeon Choi,[3] Yun Bin Lee,[4] Dong Hyun Sinn,[5] Young-Suk Lim[1]

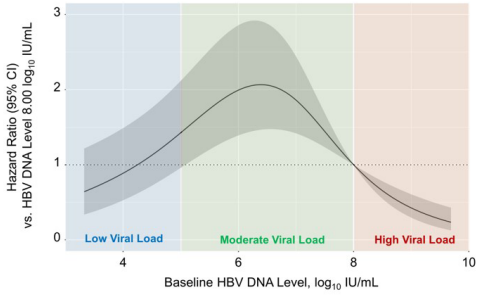
[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Republic of Korea, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam-si, Gyeonggi-do, Republic of Korea, [4]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [5]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: The association between baseline pre-treatment serum hepatitis B virus (HBV) DNA levels and on-treatment hepatocellular carcinoma (HCC) risk remains controversial in chronic hepatitis B (CHB) patients. We aimed to investigate the association between baseline HBV viral load and on-treatment HCC risk in non-cirrhotic CHB patients.

Methods: In this multicenter cohort study, on-treatment HCC risk was analyzed in 4,693 non-cirrhotic adult patients with HBeAg-negative and HBeAg-positive CHB treated with entecavir or tenofovir from 5 centers in South Korea. Baseline HBV DNA level was analyzed as a categorical variable.

Results: During a median of 7.6 years of antiviral treatment, 193 patients developed HCC (0.53 per 100 person-years). Baseline HBV DNA level was independently associated with on-treatment HCC risk in a non-linear, parabolic pattern. Patients with moderate baseline viral loads (5.00–7.99 $\log_{10}$ IU/mL) exhibited the highest HCC risk (HR, 2.60; $p<0.001$), followed by those with low viral loads (3.30–4.99 $\log_{10}$ IU/mL; HR, 1.66; $p=0.11$). *Patients with high viral loads (≥8.00 $\log_{10}$ IU/mL)* presented the lowest HCC risk. Particularly, patients with baseline HBV DNA levels 6.00–6.99 $\log_{10}$ IU/mL had the highest on-treatment HCC risk (HR, 3.36; $p<0.001$) compared to those with baseline HBV DNA levels ≥8.00 $\log_{10}$ IU/mL. These findings were more prominent among younger patients (<45 years) and those with less advanced hepatic fibrosis.

Figure. Adjusted hazard ratio for the on-treatment HCC risk by baseline HBV DNA levels in CHB patients treated with entecavir or TDF.
Hazard ratio plot adjusted for age, sex, platelet count, HBeAg-positivity, levels of ALT, and FIB-4 index with HBV DNA level of 8.00 $\log_{10}$ IU/mL as a reference.
The black line represents the point estimates, and the gray zone indicates 95% confidence intervals.
ALT, alanine aminotransferase; CHB, chronic hepatitis B; FIB-4, fibrosis-4; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.



Conclusions: Patients with moderate baseline viral load, particularly around 6 $\log_{10}$ IU/mL, demonstrated the highest on-treatment HCC risk, despite long-term antiviral treatment. Early initiation of antiviral treatment, tailored to viral load, should be considered to minimize HCC risk in non-cirrhotic adult CHB patients.

Keywords: HBV DNA, Liver cancer, Nonlinear, Parabolic, Prevention

Oral Poster Group 4. [HCC]

OP-19

Risk of Variceal Bleeding in Patients Receiving Atezolizumab–Bevacizumab Treatment for Hepatocellular Carcinoma

Kanghee Park*[1], Euichang Kim*[1], Hye Won Lee*[2], Won-Mook Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1], Changhoon Yoo[3], Sook Ryun Park[3], Min-Hee Ryu[3], Baek-Yeol Ryoo[3], Jonggi Choi[1]

[1]Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: IMbrave 150 study excluded patients with a history of variceal bleeding (VB) or high-risk varices. We assessed the real-world risk of VB in patients with hepatocellular carcinoma (HCC) receiving atezolizumab–bevacizumab treatment and identified the risk factors for VB bleeding.

Methods: We retrospectively analyzed data from 456 HCC patients who underwent endoscopy before atezolizumab–bevacizumab treatment at two hospitals in Korea. Primary outcome was the occurrence of VB. Patients were randomly divided into a training (n=320) and a validation set (n=136). We developed a prediction model using the training cohort and evaluated its performance in the validation set.

Results: In the training set, VB occurred in 15 (4.7%) patients during a median follow-up of 5.0 months. The cumulative VB rates in the training set were 2.3%, 5.2%, and 8.2% at 3, 6, and 12 months, respectively. A platelet <100,000/mm^3, portal vein invasion (PVI), and varices needing treatment (VNT) on pretreatment endoscopy were significantly associated with an increased risk of VB. Patients categorized into low (no risk factor), intermediate (1 risk factor), and high-risk (≥2 risk factors) groups had VB risks of 0%, 5.9%, and 14.5% at 6 months, respectively. Our prediction model, named 'PV 100', exhibited time-dependent AUROC of 0.810 and 0.829 for the risk of VB at 6 and 12 months, respectively in the training set. The time-dependent AUROC for the PV100 model in the validation set were 0.841, and 0.935, corresponding to the 6- and 12-month risk of VB, respectively.

Conclusions: A low platelet count, PVI, and VNT increased the risk of VB after atezolizumab–bevacizumab treatment for HCC. We developed a high-performing prediction model, 'PV100', to assess VB risk.

Keywords: Atezolizumab, Bevacizumab, Hepatocellular carcinoma, Variceal bleeding

OP-20

Association of Proton Pump Inhibitors and the Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients: A Korean Nationwide Cohort Study

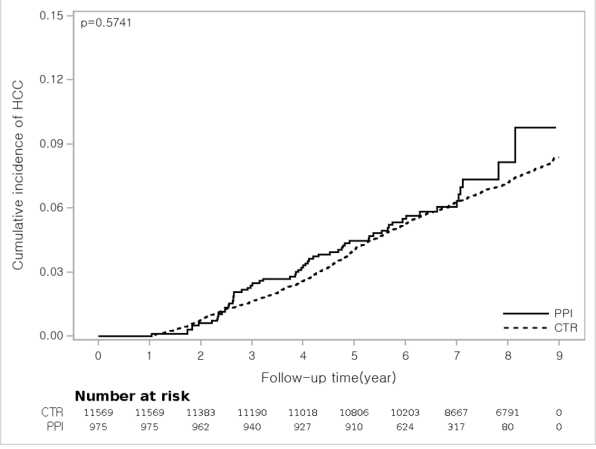
Young Youn Cho[1], Eunju Kim[2], Jong-In Chang[2], Hyung Jun Kim[1]

[1]Department of Internal Medicine, Chung-Ang University Hospital, [2]Department of Internal Medicine, Chung-Ang University GwangMyeong Hospital

Aims: Long term proton pump inhibitors (PPI) can be associated with various gastrointestinal cancers. Association of PPI use and hepatocellular carcinoma (HCC) was controversial in previous studies.

Methods: We analyzed 12,544 chronic hepatitis B (CHB) patients in the Korean National Health Insurance Service database from 2009 to 2012. Patients using H2-receptor antagonist were excluded. Multivariable cox regression and 1:5 propensity score (PS) matching were performed.

Results: In the total cohort 975 patients were included in the PPI group, 11,569 patients were included in the non-user group. After mean 7.4 years of follow up, 60 (6.15%) patients developed HCC in the PPI group, and 840 (7.26%) patients developed HCC in the non-user group. PPI was not associated with HCC development in the multivariable analysis (adjusted hazard ratio (HR), 1.169; 95% confidence interval (CI), 0.897–1.524; P value=0.248). In the PS matched cohort, PPI was still not associated with HCC development (HR, 1.129; 95% CI, 0.855–1.49; P value=0.392).



Conclusions: In our study, PPI use was not associated with HCC development in CHB patients.

Keywords: Proton pump inhibitor, Chronic hepatitis B, Hepatocelluar carcinoma

OP-21

Effects of Hepatocellular Carcinoma Screening Test on Survival in the Elderly Patients

Aryoung Kim[1], Byeong Geun Song[1], Myung Ji Goh[1], Wonseok Kang[1], Dong Hyun Sinn[1], Geum-Youn Gwak[1], Yong-Han Paik[1], Moon Seok Choi[1], Joon Hyeok Lee[1]

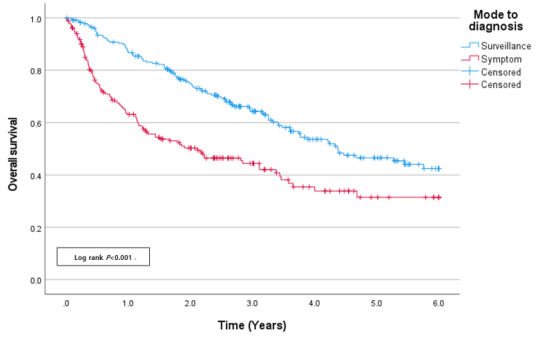
[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Screening for hepatocellular carcinoma (HCC) in patients with chronic liver disease is recommended from international guidelines to improve early tumor diagnosis and survival. However, it has not been studied whether cancer screening has advantages even in elderly patients. The purpose of this study is to determine the survival benefits of screening for HCC in elderly individuals.

Methods: This is a single-center retrospective cohort study of HCC patients over the age of 75 diagnosed between January 2009 and December 2021. Those diagnosed with screening (n=235) were compared to those diagnosed with symptoms (n=184) in overall cohort. A subgroup analysis was also carried out, stratified by patients aged 75-79 years old and over 80 years. The Kaplan-Meier method was used to calculate overall survival (OS). A Cox proportional hazards model was used for multivariate analysis.

Results: In overall cohort, the screening group had better Eastern Cooperative Oncology Group (ECOG) performance (ECOG 0; 78.7% vs. 60.9%, p<0.001), had more viral etiology (63.4% vs. 29.4%, p<0.001), and was more likely to be diagnosed with modified Union for International Cancer Control (mUICC) stage 1 or 2 (72.3% vs. 39.1%, p<0.001) than the symptom group. The OS survival in screening group was better than in symptom group (median 4.4 vs. 2.1 years, log rank p<0.001) In multivariate analysis (excluding HCC stage), screening was significantly associated with better survival (aHR 0.64, 95% CI 0.47-0.87, p=0.004). Even in the analysis including HCC stage, screening showed a correlation with better survival, but statistically significance decreased (aHR 0.74, 95% CI 0.54-1.02, p=0.07). In subgroup analysis, the OS of patients aged 75-79 who received screening was significantly better (median 5.3 vs. 2.2 years, log rank p<0.001), and the OS of patients aged over 80 also tended to be better (median 3.3 vs. 1.8 years, log rank p=0.05).

Figure. Kaplan-Meier estimates of survival in elderly patients according to mode to diagnosis (over 75 years)



Surveillance	235	195	152	104	66	44	23
Symptom	184	104	71	42	23	11	6

Conclusions: Even in the elderly, performing HCC screening tests improves survival. Early detection through screening tests is believed to play a major role in improving survival rates.

Keywords: Screening test, Hepatocellular carcinoma, Elderly

OP-22

Clinico-Pathological Characterization of hTERT-Telomere Abnormalities in Hepatocellular Carcinoma

Jung Eun Jang[2] Jin Seoub Kim[2], Hye Seon Kim[2], Ji Min Kim[2], Jung Hyun Kwon[1], Ji Won Han[1], Pil Soo Sung[1], Si Hyun Bae[1], Jong Young Choi[1], Seung Kew Yoon[1], Jeong Won Jang[1*]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, [2]The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, Department of Biomedicine & Health Sciences, Graduate School, The Catholic University of Korea, Seoul

Aims: Human telomerase reverse transcriptase (TERT) genetic alterations play an essential role in hepatocarcinogenesis. However, the crosstalk of TERT promoter mutation, TERT expression, and telomere length (TL) in hepatocellular carcinoma (HCC) are not fully understood. The aim of the study is to investigate the association of TERT-telomere abnormalities with clinic-pathologic findings in patients with HCC.

Methods: The study recruited a total of 222 HCC patients and 95 non-tumor patients with biopsied liver tissues. We detected TERT promoter mutation, TERT expression, and TL by Sanger sequencing and quantitative real-time PCR. The integrative analysis of TERT-telomere alterations and TL was performed in relation to the clinico-pathological findings of HCC.

Results: TERT alterations were more frequently observed in tumors than in paired non-tumor tissues. Regarding the etiology of liver disease, TERT expression was highest in HBV-associated HCCs,and TERT promoter mutations were more frequently present in non-HBV-associated HCCs than in HBV-associated HCCs. TERT overexpression was associated with high tumor burden, with its higher expression with a larger tumor, tumor multiplicity, and portal vein invasion or metastasis. Moreover, TERT expression positively correlated with grade of tumor differentiation and stage progression for both the mUICC and BCLC stages. In contrast, TL tended to be shortened with high tumor burden, with a negative correlation of TL with tumor differentiation and HCC stage progression. Unlike TERT expression or TL, there was no association between TERT promoter mutations and tumor stage or tumor grade.

Conclusions: The study recruited a total of 222 HCC patients and 95 non-tumor patients with biopsied liver tissues. We detected TERT promoter mutation, TERT expression, and TL by Sanger sequencing and quantitative real-time PCR. The integrative analysis of TERT-telomere alterations and TL was performed in relation to the clinico-pathological findings of HCC.

Keywords: Liver cancer, Telomere, Biomarker, Pathology

OP-23

Artificial Intelligence Model to Predict De Novo Hepatocellular Carcinoma after 5 Years of Antiviral Therapy

Yeonjung Ha[1], Young Eun Chon[1], Joo Ho Lee[1], Prof. Kwan Sik Lee[1], Jinseok Lee[2], Prof. Han Chu Lee[3]

[1]CHA Bundang Medical Center, CHA University, [2]Kyung Hee University, [3]Asan Medical Center

Aims: Patients with chronic hepatitis B (CHB) receiving potent antiviral agent, such as entecavir (ETV) or tenofovir (TFV), achieve virological and biochemical stability after long-term (>5 years) therapy. Prediction of de novo hepatocellular carcinoma (HCC) in these patients is particularly important considering limited medical resources and relatively lower incidence of HCC compared with those treated for <5 years. Therefore, we aimed to construct an individualized artificial intelligence (AI) model to predict de novo HCC after 5 years of ETV/TFV therapy.

Methods: From retrospective registry data from two university hospitals, 5,908 and 562 patients with CHB who were treated with ETV/TFV for > 5 years and were not diagnosed with HCC during the first 5 years of therapy were selected, respectively. A total of 37 variables including baseline characteristics (age, sex, cirrhosis, and type of antiviral agent), laboratory parameters (albumin, bilirubin, prothrombin time, transaminases, platelet counts, HBeAg, HBV DNA, and Child-Pugh score) at baseline and at 5 years, aspartate aminotransferase to platelet ratio at 5 years, and derived time-varying variables (change in laboratory parameters) were used as input variables. From the training set (n=4,726), we applied five machine learning algorithms based on 100 datasets derived from repeated 5-fold cross-validation, including adaptive boosting, extreme gradient boosting, light gradient boosting machine, logistic regression, and random forest classifier. Internal validation was performed in a split dataset (n=1,182). The final model was tested in patients from another university hospital as external validation (n=562).

Results: In the training set, logistic regression showed the highest area under the receiver operating curve (AUROC) of 0.803 and balanced accuracy of 0.735, which outperformed other AI algorithms (AUROC, 0.775-0.802 and balanced accuracy, 0.701-0.729). The sensitivity and specificity were 75.3% and 71.6%, respectively. An ensemble approach by soft voting technique demonstrated that the combined model with logistic regression and random forest classifier provided the best performance (AUROC, 0.811 and balanced accuracy, 0.754). The results derived from the test set also showed good performance metrics (AUROC, 0.784 and balanced accuracy, 0.712). In the external validation, our model showed an AUROC of 0.862 and balanced accuracy of 0.771. A web-based calculator was developed.

Conclusions: Our AI model combining logistic regression and random forest classifier provides good performance in predicting de novo HCC occurrence after 5 years of ETV/TFV therapy. It can compute the estimated risk of HCC and facilitate individualized HCC surveillance based on risk stratification.

Keywords: Chronic hepatitis B, Hepatocellular carcinoma, Prediction, Artificial intelligence

OP-24

Modified Albumin-Bilirubin Grade after Curative Treatment: Risk Prediction of Late Intrahepatic Recurrence of Hepatocellular Carcinoma

Jeong Il Yu[1], Hee Chul Park[1], Bong Kyung Bae[2], Myung Ji Goh[3], Moon Seok Choi[3], Jinsoo Rhu[4], Min Woo Lee[5], Woo Kyoung Jeong[5], Minji Kim[6], Kyunga Kim[6]

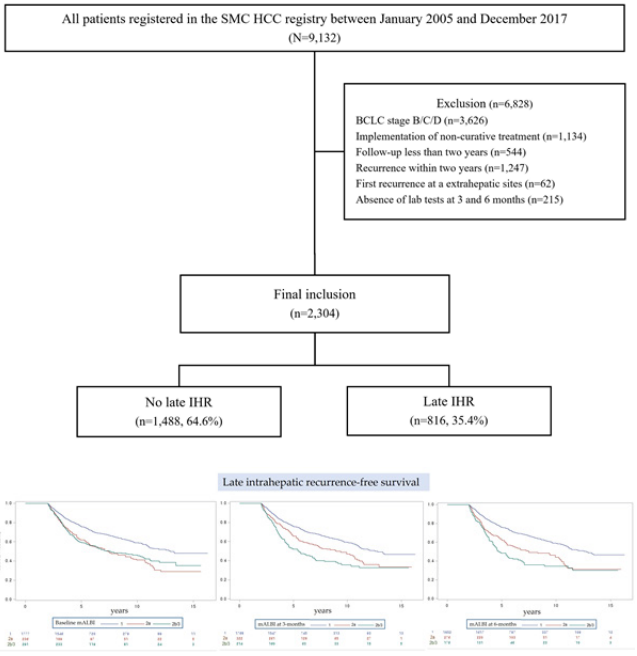
Departments of [1]Radiation Oncology, [3]Medicine, [4]Surgery, [5]Radiology, Sam-

sung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [2]Department of Radiation Oncology, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea, [6]Statistics and Data Center, Samsung Medical Center, Research Institute for Future Medicine, Seoul, Korea

Aims: We aimed to identify prognostic factors for late intrahepatic recurrence (IHR) defined as recurrence more than 2 years after curative treatment in newly diagnosed hepatocellular carcinoma (HCC).

Methods: This study was conducted with the subject of newly diagnosed, previously untreated, very early or early HCC treated with initial curative treatment, and followed up without recurrence for more than 2 years. Late IHR-free survival (IHRFS) was defined as the time interval from initial curative treatment to the first IHR or death without IHR, whichever came first.

Results: Among all the enrolled patients, 1,427 (61.9%) patients underwent curative intent hepatectomy, and the remaining 877 (38.1%) patients underwent local ablative therapy (LAT). During the follow-up after curative treatment (median 82.6 months, range 24.1 to 195.7), late IHR was detected in 816 (35.4%) patients. In the multivariable analysis, age, male sex, type of initial treatment, and modified albumin-bilirubin (mALBI) grade were significant prognostic factors as a baseline factors. And, mALBI grade at 3-months (2a vs 1, p=0.001, hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.15-1.76; 2b/3 vs 1, p<0.001, HR 1.67, 95% CI 1.28-2.17) and 6-months (2a vs 1, p=0.004, HR 1.43, 95% CI 1.12-1.81; 2b/3 vs 1, p<0.001, HR 1.79, 95% CI 1.32-2.44) after initial curative treatment was also significant prognostic factors of late IHR .



Conclusions: After curative treatment in newly diagnosed early HCC, mALBI grade at 3-months and 6-months after initial curative treatment as well as baseline was one of the most crucial prognostic factor for late IHR.

Keywords: Liver cancer, Recurrence, Curative treatment, Prognostic factor

Poster Exhibition

[Alcoholic Liver Disease]

PE-01

Characteristics of Microbiome-Derived Metabolomics according to the Progression of Alcoholic Liver Disease

Raja Ganesan, Satya Priya Sharma, Sang Jun Yoon, Dong Joon Kim, Ki Tae Suk*

Institute for Liver and Digestive Diseases, College of Medicine, Hallym University, Chuncheon 24252, Republic of Korea

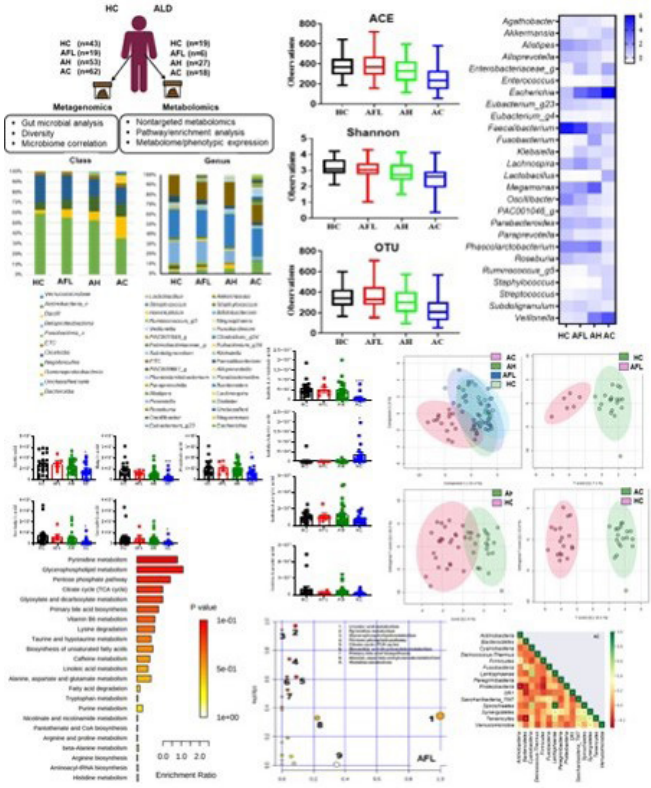
Aims: The prevalence and severity of alcoholic liver disease (ALD) are increasing. The incidence of alcohol-related cirrhosis up to 2.5 %. This study aimed to identify novel metabolite mechanisms involved in the development of ALD in patients. The use of gut microbiome-derived metabolites is increasing in targeted therapies. Identifying metabolic compounds is challenging due to the complex patterns that have long-term effects on ALD. We investigated the specific metabolite signatures in ALD patients.

Methods: This study included 247 patients (heathy control, HC: n=62, alcoholic fatty liver, AFL; n=25, alcoholic hepatitis, AH; n=80, and alcoholic cirrhosis, AC, n=80) were identified, and stool samples were collected. 16S rRNA sequencing and metabolomics were performed with MiSeq sequencer and liquid chromatography coupled to time-of-flight–mass spectrometry (LC–TOF-MS), respectively. The untargeted metabolites in AFL, AH, and AC samples were evaluated by multivariate statistical analysis and metabolic pathotypic expression. Metabolic network classifiers were used to predict the pathway expression of the AFL, AH, and AC stages.

Results: The relative abundance of *Proteobacteria* was increased and the abundance of *Bacteroides* was decreased in ALD samples (p=0.001) compared with that in HC samples. *Fusobacteria* levels were higher in AH samples (p=0.0001) than in HC samples. Untargeted metabolomics was applied to quantitatively screen 103 metabolites from each stool sample. Indole-3-propionic acid levels are significantly lower in AH and AC (vs. HC, p=0.001). Indole-3-lactic acid (ILA: p=0.04) levels were increased in AC samples. AC group showed an increase in indole-3-lactic acid (vs. HC, p=0.040) level. Compared with that in HC samples, the levels of short-chain fatty acids (SCFAs: acetic acid, butyric acid, propionic acid, iso-butyric acid, and iso-valeric acid) and bile acids (lithocholic acids) were significantly decreased in AC. The pathways of linoleic acid metabolism, indole compounds, histidine metabolism, fatty acid degradation, and glutamate metabolism were closely associated with ALD metabolism.

Conclusions: This study identified that microbial metabolic dysbiosis is associated with ALD-related metabolic dysfunction. The SCFAs, bile acids, and indole compounds were depleted during ALD progression. Clinical trial Clinicaltrials.gov, number NCT04339725.

Keywords: Alcoholic liver disease, Microbiome, Metabolomics, Metabolic discriminations, Metagenomics



PE-02

Gut-Microbiota Prompted Activation of Natural Killer Cell on Alcoholic Liver Disease

Jung A Eom, Sang Jun Yoon, Kyeong Jin Lee, Byeong Hyun Min, Min Kyo Jeong, Jin-Ju Jeong, Sung Min Won, Haripriya Gupta, SatyaPriya Sharma, Raja Ganesan, Ki Tae Suk*

Institute for Liver and Digestive Disease, Hallym University College of Medicine, Chuncheon, Korea

Aims: The liver is rich in innate immune cells such as natural killer (NK) cells, natural killer T (NKT) cells, and Kupffer cells related to the gut microbiome. These immune cells are dysfunctional due to alcohol consumption. However, there are insufficient data on the association of immune cells and gut microbiota in alcoholic liver disease (ALD). Therefore, the purpose of this study is to evaluate the effect of candidate strains on NK cells in ALD.

Methods: A total of 125 human blood samples [control (n=22), alcoholic hepatitis (n=43) and alcoholic cirrhosis (n=60)] were collected for flow cytometry. C57BL/6J mice were divided into 4 groups (normal, EtOH fed group, 2 EtOH+strain groups). *P. dorei* and *L. helveticus* were administered orally 3 times/week for 10 weeks at a concentration of 109 CFU/mouse. Lymphocytes isolated from mouse liver were analyzed by flow cytometry.

Results: The frequency of NK cells increased in patients with alcoholic hepatitis and decreased in patients with alcoholic cirrhosis. The expression of NKp46, an activating receptor for NK cells, decreased in alcoholic hepatitis patients and increased in alcoholic liver cirrho-

sis patients compared to the healthy controls. Cytotoxic CD56dim-CD16+ NK cells were significantly reduced in patients with alcoholic cirrhosis. We tested the effect by orally administering *P. dorei* and *L. helveticus* to EtOH-fed mice. *P. dorei* and *L. helveticus* reduced the inflammatory cytokines increased by EtOH supply and increased the expression of NKp46, granzyme B, and perforin, which were decreased by EtOH supply.

Conclusions: Alcohol intake reduces the cytolytic activity of NK cells, innate immune cells that play a central role in the liver. However, *P. dorei* and *L. helveticus* ameliorate alcohol-induced liver inflammation and enhance the reduced NK cell activity in experimental ALD livers. Therefore, these observations suggest that the gut microbiota can improve alcoholic liver disease by modulating immune cells.

Keywords: Alcoholic liver disease, Immune, Gut microbiota, NK cell

PE-03

Dose-Response Relationship between Alcohol Consumption and Incidence of Liver Disease : A Nationwide Cohort Study

Sang Yi Moon[1], Yang Hyun Baek[1], Yeo Wool Kang[1], Min Kook Son[2]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea, [2]Department of Physiology, College of Medicine, Dong-A University, Busan, Republic of Korea

Aims: Alcohol is a contributing factor to a variety of diseases, including liver disease, cancer, diabetes, hypertension, dementia, and depression. Gender, race, malnutrition, obesity, and coexisting liver disease play a role in alcohol-related liver disease, but excessive alcohol consumption is the most important factor. Although most patients with alcohol-related liver disease have a long and heavy history of alcohol use, it is still uncertain whether the total amount of alcohol consumption contributes to the development of the disease. We investigated the dose-response relationship between alcohol consumption and the incidence of liver-related diseases.

Methods: Using the Korean National Health Insurance database, we recruited patients aged 40 years and older who had undergone at least two health examinations between 2009 and 2012 and followed them until December 31, 2019. Participants with conditions that could potentially cause liver disease other than alcohol-related, such as viral, toxic, and infectious hepatitis, and gallbladder and bile duct disease, were excluded from the study. In addition, individuals with pre-existing liver disease prior to the study period and those with missing data were also excluded. The primary outcome was newly diagnosed liver-related disease within the observation period, and the association between alcohol consumption and liver-related disease was determined using multivariable Cox proportional hazards regression analysis.

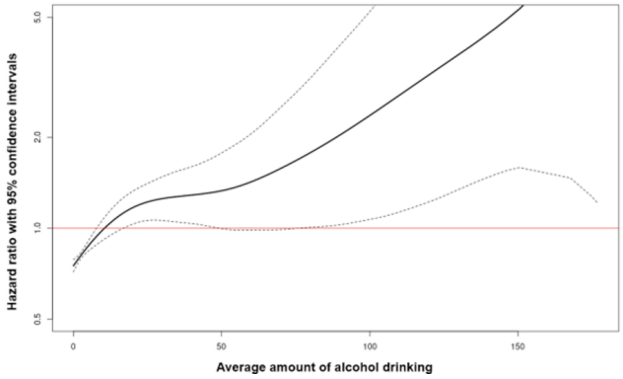
Results: A total of 59,128 patients were enrolled and followed for a median of 7.5 years, during which time 1,519 cases of liver-related disease occurred. The participants were divided into two groups: abstainers and drinkers. Among the drinkers, four quantiles (Q1, Q2, Q3, and Q4) were identified based on the average amount of alcohol consumed per week. The corresponding number of glasses of alcohol consumed per week for each quantile (Q1, Q2, Q3, and Q4) was labeled 1.8±1.1 standard units (1 standard unit=8g alcohol), 5.1±2.1 standard units, 10.4±3.9 standard units, and 24.6±14.6 standard units, respectively. Compared with non-drinkers, the risk of liver-related disease was found to be higher in Q1 drinkers (adjusted hazard ratio [aHR], 1.06; 95% CI, 0.88-1.27), Q2 drinkers (aHR, 1. 18; 95% CI, 0.99-1.40), Q3 drinkers (aHR, 1.31; 95% CI, 1.10-1.55), and Q4 drinkers (aHR, 1.50; 95% CI, 1.27-1.76). The restricted cubic spline curve shows the continuous change between alcohol consumption and liver-related disease, and similar to the main analysis, we found that the risk of liver-related disease increased with total alcohol consumption.

Table 1. Hazard ratio and 95% confidence interval for incidence of liver-related diseases according to average amount of alcohol drinking

	Events	Follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Hazard ratio (95% confidence intervals)			
				Crude	P-value	Adjusted*	P-value
All subjects (n = 59,128)							
No	640	210,900	3.03	1.00 (reference)		1.00 (reference)	
Q1	168	57,810	2.91	0.96 (0.81-1.13)	0.61	1.06 (0.88-1.27)	0.55
Q2	199	59,438	3.35	1.10 (0.94-1.29)	0.25	1.18 (0.99-1.40)	0.06
Q3	226	59,190	3.82	1.26 (1.08-1.46)	0.003	1.31 (1.10-1.55)	0.002
Q4	286	58,112	4.92	1.60 (1.40-1.84)	< 0.001	1.50 (1.27-1.76)	< 0.001

Average alcohol consumption (standard units per week) Q1: 1.8 ± 1.1 standard units, Q2: 5.1 ± 2.1 standard units, Q3: 10.4 ± 3.9 standard units, Q4: 24.6 ± 14.6 standard units

Figure 1. Restricted cubic spline of hazard ratio with 95% confidence intervals for liver-related diseases according to average amount of alcohol drinking.



Conclusions: There was a positive correlation between the average amount of alcohol consumed per week and the incidence of liver disease. A significant increase in liver-related diseases was found in the group that consumed small amounts of alcohol (83.2±31.2 g/week) compared to the abstinence group.

Keywords: Alcohol, Liver-realted disease

[Hepatitis A/E: Basic and Translational Research]

PE-04

A Newly Developed in-House Double Antigen Sandwich ELISA for Detection of Anti-HEV IgG among Pregnant Women in Cambodia

Ulugbek Mirzaev[1,2], E Bunthen[1,3], Serge Ouoba[1,4], Ko Ko[1], Aya Sugiyama[1], Tomoyuki Akita[1], Kazuaki Takahashi[1], Junko Tanaka[1]

[1]Department of Epidemiology, Infectious Disease Control and Prevention,

Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan, [2]Department of Hepatology, Research Institute of Virology, Tashkent, Uzbekistan, [3]Payment Certification Agency (PCA), Ministry of Health, Phnom Penh, Cambodia, [4]Unité de Recherche Clinique de Nanoro (URCN), Institut de Recherche en Sciences de La Santé (IRSS), Nanoro, Burkina Faso, Japan

Aims: Hepatitis E virus (HEV) infection poses a significant public health challenge, particularly in developing countries where pregnant women are more susceptible to complications arising from the infection. Cambodia has a notable prevalence of HEV infection (18.4%), with sporadic outbreaks observed throughout the nation. The aim of this study is to develop an affordable in-house ELISA method that could be useful for resource-limited settings and to determine anti-HEV prevalence among pregnant women in Siem-Reap, Cambodia.

Methods: This is a continuum of study on hepatitis B mother-to-child transmission conducted in Siem Reap, Cambodia from February 2020 to December 2021. The in-house double antigen Sandwich ELISA method was developed to detect anti-HEV IgG. To validate in-house ELISA, 184 pregnant women's serums randomly selected among an overall 1565 were tested with commercial test systems RecomLine HEV IgG (Mikrogen GmbH, Germany), IgG anti-HEV EIA (Institute of Immunology, Japan) and in-house ELISA.

Results: The number of anti-HEV IgG-positive samples detected by Mikrogen, Institute of Immunology, and in-house ELISA test systems were 41, 25, and 33 samples, respectively. In-house ELISA provided 92.39% agreement with a Cohen's kappa coefficient of 0.76 to RecomLine Mikrogen but 89.13% to the Institute of Immunology Co. Ltd test system with a kappa coefficient of 0.59.

Conclusions: In conclusion, In-house developed ELISA demonstrates a higher agreement to the RecomLine HEV IgG (Mikrogen GmbH, Germany) than the IgG anti-HEV EIA (Institute of Immunology Co., LTD, Japan). This finding supports that our double antigen Sandwich ELISA method has good sensitivity and specificity, indicating its potential as a reliable screening tool. Further, we planned to test all 1565 samples by the In-house ELISA method and will present the results at the conference.

Keywords: Hepatitis E, Cambodia, Siem Reap, Seroprevalence, Pregnant women, In-house ELISA

PE-05

The Seroprevalence of Hepatitis E Virus in the Ethnic Minorities of Ha Giang Province, Vietnam

Lichnaia E.[1], Bui Thi Thanh Nga[2], Pham Thi Ha Giang[2], Starkova D.[1], Petrova O.[1], Bui Thi Lan Anh[2], Tran Thi Nhai[2], Vo Viet Cuong[2], Pham Ngoc Quang[2], Dmitriev A.[3,4], Kalinina O.[1,5]

[1]Saint-Petersburg Pasteur Institute, Saint-Petersburg, Russia, [2]Joint Russian-Vietnamese Tropical Science and Technology Center, Hanoi, Vietnam, [3]Federal State Budgetary Scientific Institution 'Institute of Experimental Medicine', Saint-Petersburg, Russia, [4]St. Petersburg State University, Saint-Petersburg, Russia, [5]Almazov National Medical Research Centre, Saint-Petersburg, Russia

Aims: Hepatitis E is an actual public health problem in Vietnam. The aim of this study was to investigate HEV seroprevalence in ethnic groups of the high-mountainous province of Ha Giang, Vietnam.

Methods: The seroepidemiological cross-sectional study included 300 indigenous people (men - 109, women - 191) aged 18-70 years (the mean age 44.4±11.7 years) from two districts Vị Xuyên, Bắc Quang, Ha Giang. The northern province of Ha Giang has a multi-ethnic composition of the population. Almost 90% of the Ha Giang population belongs to various ethnic minorities. In our study, the majority of the participants belonged to two ethnic groups Tay (47.0%) and Dao (45.0%). National minorities were also represented: Pà Thẻn, Kinh, Nùng, Khơ mú. Specific antibodies to HEV (anti-HEV IgG and anti-HEV IgM) were tested by ELISA Russian-made kits according to the manufacturer's instructions.

Results: Totally, the prevalence of anti-HEV IgG was 63.0% (189/300; 95% CI 57.4-68.3), anti-HEV IgM - 10.3% (31/300; 95% CI 7.4-14.3), both anti-HEV IgG and anti-HEV IgM were found in 8.7% (26/300; 95% CI 6.0-12.4) cases. Among the participants of the Tay ethnic group anti-HEV IgG was detected in 63.1% (89/141; 95% CI 54.9-70.6), anti-HEV IgM - 8.5% (12/141; 95% CI 4, 9-14.3). Among the participants of the Dao ethnic group anti-HEV IgG was detected in 62.2% (84/135; 95% CI 53.8-70.0), anti-HEV IgM - 12.6% (17/135; 95% CI 8.0-19.2). Among the participants of other ethnic minorities (Pà Thẻn, Kinh, Nùng, Khơ mú), the presence of anti-HEV IgG was 66.7% (16/24; 95% CI 46.7-82.0), anti-HEV IgM - 8, 3% (2/24; 95% CI 2.3-25.9).

Conclusions: The obtained results indicate a high seroprevalence of HEV infection among different ethnic minorities of Ha Giang Province, regardless of ethnicity.

Keywords: Hepatitis E virus, Vietnam, Ethnic minority

[Hepatitis A/E: Clinical Aspects]

PE-06

A Silent Outbreak of Hepatitis E Virus Infection or False Positive Reaction of Anti-HEV IgM after COVID-19 Vaccination?: Epidemiological Investigation of an Outbreak in a Korean Factory Complex in 2022

Gwang Hyeon Choi[1*], Jeonghyeon Oh[2*], Yeonhwa Chang[2], Jina Kim[2], Kunhee Park[2], Hansol Yeom[3], Soonryu Seo[3], Jin Gwack[3], Sook-Hyang Jeong1[†]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173 beon-gil, Bundang-gu, Seongnam, Gyeonggi-do, Republic of Korea, [2]Gyeonggi Infectious Disease Control Center, Health Bureau, Gyeonggi Provincial Government, 30 Docheong-ro, Yeongtong-gu, Suwon City, Gyeonggi Province, Republic of Korea, [3]Division of Infectious Disease Control, Korea Disease Control and Prevention Agency, Osong Health Technology Administration Complex, 187, Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea

Aims: To investigate a reported outbreak of presumed hepatitis E virus (HEV) infection in a Korean food manufacturing facility and to explore the association between anti-HEV immunoglobulin M (IgM) positivity and COVID-19 infection or vaccination.

Methods: Twenty-four cases of anti-HEV IgM positivity were reported among 646 workers at the facility in 2022. An epidemiological investigation was conducted, comprising HEV-RNA testing of blood and environmental samples, analysis of group meal records, and an

association between anti-HEV IgM positivity and confirmed COVID-19 infection or vaccination.

Results: All 24 patients were asymptomatic, with cases spread sporadically across the facility. HEV-RNA was not detected in serum or environmental samples. Four group meals on certain days showed higher anti-HEV positivity. Although the cumulative rate of COVID-19 infection showed no difference; the anti-HEV IgM positive group showed significantly higher proportions of >2 doses of COVID-19 vaccination (83.3% vs. 48.7%, p=0.021), vaccination within 90 days (45.8% vs. 19.7%, p=0.008), and Moderna vaccine administered as the last vaccine (75% vs. 14.5%, p<0.001) than those of the anti-HEV negative group. In four multivariable models, three or more COVID-19 vaccinations and Moderna vaccine as the last vaccine were consistently associated with anti-HEV IgM positivity, while specific day group meal intake was also a significant factor.

Conclusions: This epidemiological investigation showed that anti-HEV IgM positivity may occur as a false-positive result related to COVID-vaccination over three times and use of the Moderna vaccine, although a portion of true HEV infection may not be excluded.

Keywords: Hepatitis E, COVID-19, Vaccination, Epidemiology

PE-07

Continuous Renal Replacement Therapy in Pediatric Patients with Hepatitis A Virus Associated Acute Liver Failure with Advanced Hepatic Encephalopathy-Effect on Survival

Arjun Maria, Nishant Wadhwa

Division of Pediatric Gastroenterology Hepatology and Liver Transplant, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Aims: This study was done to determine the effect of CRRT on survival in pediatric patients with HAV associated ALF with HE grade III and IV.

Methods: This was a retrospective analysis of children with HAV associated ALF with HE grade III/IV between January 2018 to April 2023. All such children were offered CRRT. Twenty one agreed to receive CRRT, whereas 14 patients who refused were treated with standard medical therapy (SMT) and included as controls. None received liver transplantation.

Results: Thirty five were analysed and 21(60%) received CRRT. Baseline characteristics were comparable apart from ammonia, which was higher in the CRRT group (p=0.001). Seven (33.3%) children in the CRRT group and 3 (21.4%) in the SMT group fulfilled the Kings College Hospital criteria for liver transplantation (p=0.445). In the CRRT group, 13 (61.9%) survived while in the SMT group 7 (50%) survived which was comparable (p=0.486). The survival time was 6.3 days in CRRT group vs 7.29 days in the SMT group which was comparable (p=0.769).
On risk predictive analysis, failure to reduce ammonia by 30% by day 3 of therapy (p=0.001), inotrope requirement at day 3 (p=0.001), higher total bilirubin values at day 3 (p=0.001) and higher ammonia at day 3 (p=0.023) and day 7 (p=0.001) were associated with mortality. On Model 1 of Cox regression analysis, which included ammonia at day 3, bilirubin at day 3 and inotrope requirement at day 3, only higher bilirubin levels were associated with mortality (Hazard Ratio 1.157, p=0.04). Since bilirubin is known to be reduced by CRRT, analysis was performed again by including CRRT and inotrope requirement in the model 2. Inotrope requirement was associated with 9.5 folds increase in mortality (Hazard ratio 9.569, p=0.001), however CRRT was not found to be significant.

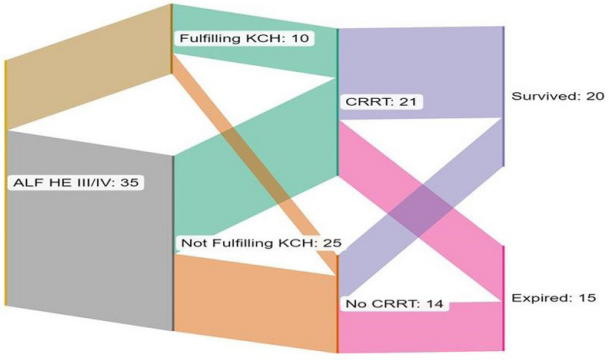


Figure 1 –Sankey plot depicting outcome of Acute Liver Failure (ALF) patients with Hepatic Encephalopathy grade III/IV (HE). Abbreviations- KCH- Kings College Hospital criteria for liver transplantation, CRRT- Continuous Renal Replacement Therapy

Table 1- Baseline characteristics of patients in continuous renal replacement (CRRT) group vs standard medical therapy (SMT) group

	CRRT (21)	SMT (14)	p Value
Age (years)	9.1	10.6	0.338*
Males	28.6%	57.1%	0.091ⁿ
Bilirubin (mg/dl)	9.68	12.08	0.415*
INR	4.69	3.33	0.128*
Ammonia (umol/L)	**273.09**	**138.27**	**0.001***
Inotrope	33.3%	28.6%	0.766ⁿ
Fulfilling KCH	33.3%	21.4%	0.445ⁿ

* Means with T Test, ⁿ percentage with chi-square test

Table 2- Survival in continuous renal replacement (CRRT) group vs standard medical therapy (SMT) group.

	CRRT (21)	SMT (14)	p Value
Survival	61.9%	50%	0.486ⁿ
7 day survival	66.7%	71.4%	0.766ⁿ
Survival time*	6.3 days	7.2 days	0.769*

* Means with T Test, ⁿ percentage with chi-square test

Conclusions: There was increased survival in children who received CRRT, however it did not reach statistical significance. High bilirubin and persisting inotropic requirement at day 3 were associated with mortality.

Keywords: Hepatitis a associated acute liver failure, Continuous renal replacement therapy, mortality, Hepatic encephalopathy grade III/IV

PE-08

Risk Factors for Development of Cirrhosis in Chronic Viral Hepatitis B Patients Who Had Persistent Viral Suppression with Antiviral Therapy

Soe Thiha Maung[1], Pakanat Decharatanachart[2], Roongruedee Chaiteerakij[1,3]

[1]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand. [2]Division of Academic Affairs, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [3]Center of Excellence for Innovation and Endoscopy in Gastrointestinal Oncology, Faculty of Medi-

cine, Chulalongkorn University, Bangkok, Thailand

Aims: Chronic viral hepatitis B (CHB)-infected patients occasionally develop cirrhosis despite having persistent viral suppression with antiviral therapy. We aimed to identify risk factors for developing cirrhosis in HBV-suppressed patients.

Methods: We conducted a case-control study of 120 non-cirrhotic CHB-infected patients who achieved viral suppression with antiviral treatment. There were 40 cases developing cirrhosis after viral suppression. Cases were 1:2 matched, by age, sex, and FIB-4 index, with 80 controls who did not develop cirrhosis during the follow-up period. We retrospectively abstracted clinical and laboratory data at the time of viral suppression, including body mass index (BMI), comorbidities, pre-treatment HBV viral load, HBe antigen status, HCV or HIV co-infection, liver chemistries, and APRI values. Risk factors for cirrhosis post-HBV suppression were identified using Cox proportional hazard analysis.

Results: Case and control groups had similar ages (51.4±9.9 vs. 51.4±10.2 years), proportions of males (80% vs. 80%) and FIB-4 values (1.32 vs. 1.31). Compared to non-cirrhosis group, cirrhosis group had a significantly greater BMI (25.1 vs. 22.7, p=0.01), more prevalence of diabetes (50.0% vs. 26.3%, p=0.01), while other comorbidities and laboratory parameters were not significantly different between the 2 groups (p>0.05). By univariate analysis, BMI >23 kg/m^2, diabetes, and APRI >0.7 were significantly associated with cirrhosis, with hazard ratios (HRs) (95% CI) of 2.99 (1.46–6.13), 2.31 (1.23–4.36), 2.71 (1.05–6.99), p=0.003, 0.010, and 0.039, respectively. In the multivariate analyses, after adjusted for APRI, BMI>23 kg/m^2 remained significantly associated with cirrhosis, with adjusted HR (95% CI) of 2.76 (1.33–5.73, p=0.006), while diabetes was borderline significantly associated with cirrhosis (aHR: 1.99, 95% CI: 0.94–4.23, p=0.072).

Conclusions: In HBV-infected patients who have viral suppression with therapy, elevated BMI and diabetes increased the risk of cirrhosis. These findings emphasize the need for early management of these factors to prevent cirrhosis development in this population.

Keywords: HBV, Cirrhosis, Obesity, Diabetes

PE-09

Hepatitis B Virus Screening Rate in Cancer Patients before Receiving Chemotherapy-A Systematic Review and Meta-Analysis

Soe Thiha Maung[1], Natee Depan[2], Pakanat Decharatanachart[2], Roongruedee Chaiteerakij[1,3]

[1]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand. [2]Division of Academic Affairs, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [3]Center of Excellence for Innovation and Endoscopy in Gastrointestinal Oncology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Aims: Screening for hepatitis B virus (HBV) infection before systemic chemotherapy administration is essential to identify patients requiring antiviral prophylaxis for HBV reactivation. We examined the HBV screening rate among cancer patients before undergoing chemotherapy.

Methods: A systematic review and meta-analysis were conducted to investigate the practice of pre-chemotherapy HBV screening. We searched for studies reporting HBV screening rates in cancer patients before chemotherapy in PubMed, Embase, Scopus and Google Scholar databases. The pooled screening rate was estimated using random effects model. Subgroup analyses were performed by study period, HBV endemic regions, malignancy types, and chemotherapy regimens.

Results: The meta-analysis included 29 studies published between 2010 and 2021. Most were conducted in the United States (n=11), followed by Australia and Taiwan (n=4), and Japan (n=3). There were 3, 6, and 7 studies conducted in low, intermediate, and high endemic regions of HBV; 21 and 15 studies reporting screening rates for hematologic and solid-organ malignancies, respectively; with 9, 7 and 8 studies of rituximab-containing regimen, regimens without rituximab, and both, respectively. The pooled screening rate was 56% (95% CI: 46%-65%, I^2=100%) (Figure). The highest HBV screening rate was observed during the year 2011-2015, reaching 69% (95% CI: 54%-81%), likely due to the increased global access to rituximab, and decreased to 60% (95% CI: 43%-75%) during 2016-2020. The screening rates for low, intermediate, and high endemic regions were 42% (95% CI: 33%-52%), 74% (95% CI: 58%-85%), and 64% (95% CI: 39%-83%), respectively. Japan exhibited the highest screening rate of 90% (95% CI: 66%-98%), followed by Taiwan (78%, 95% CI: 53%-98%). Patients with hematologic malignancies displayed a higher screening rate (67%; 95% CI: 57%-76%) than those with solid organ tumors (36%; 95% CI: 20%-56%).

Conclusions: Despite existing guidelines, pre-chemotherapy HBV screening rate remains unsatisfactory, with substantial heterogeneous rates globally. These findings underscore the need for effective strategies to align practices with clinical guidelines.

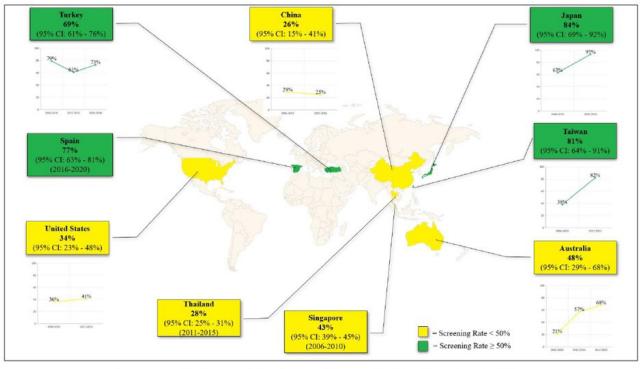


Figure 1: Geographical presentation of Screening rates of countries included in the meta-analysis

Keywords: HBV, Screening rate, Chemotherapy, Clinical practice guidelines

[Hepatitis B: Basic and Translational Research]

PE-10

The Prevalence of Genotypes and Subtypes of HBV in Kazakhstan

Balzhan Abzhaparova

The Department of Hepatopancreatobiliary Surgery and Liver Transplantation of the A.Syzganov's National Scientific Center of Surgery, Almaty, Kazakhstan

Aims: The purpose of the study: to study the prevalence of genotypes and subtypes of HBV in Kazakhstan

Methods: Blood samples of patients were examined for the determination of genotypes and subtypes of HBV by the PCR. Isolation of HBV DNA was performed using the GeneJETViral DNA. Purification Kit, ThermoScientific, PCR was performed using specific primers. Purified PCR products were sequenced in two directions, using a forward and reverse primer

Results: Total 834 patients chronic hepatitis B patients were inclided to the study from November 2-17 to June 2019. The study subjects were admitted for treatment in the regional hepatological Centers from 13 cities of Kazakhstan. 341 samples were positive for PCR and genotyped of HBV. Comparison and phylogenetic analysis of nucleotide sequences of HBV isolates showed that they are represented by genotypes HBV-D (95.9%), HBV-A (3.5%) and HBV-C (0.6%). At the same time, the identity of the nucleotide sequences of RK isolates was: HBV-D (95-100%); HBV-A (97.2-100%) and HBV-C (99%) in Kazakhstan.

Conclusions: The chronic viral hepatitis B in the Republic of Kazakhstan is associated with: HBV genotype D in 91.3%, Genotype A in 7.7%, Genotype C in 1.0%. Among patients with chronic hepatitis B with D, the highest frequency of occurrence of the subgenotype D1 (61.5%), D2 - 10.6%, D3 - 9.6%. Analysis of the results of hepatitis B virus genotyping according to a study of 10 regions of Kazakhstan showed that in 91.3% of HBV it has genotype D. Only 7.7% of cases were identified genotypes A and 1.0% - genotype C of hepatitis B virus In 21 patients positive HBV DNA and HDV RNA PCR detected Hepatitis B virus genotype D. In the study of hepatitis B virus subgenotypes, we found that the most common subgenotype is D1-61.5%.

Keywords: Hepatites B, Genotypes and subtypes of HBV, Liver cirrosis, Genotype

PE-11

Risk Factors for Hepatitis B Incidence in Pregnant Women in Indonesia: A Literature Review

Rinita Istiqomah

Yogyakarta State University, Indonesia

Aims: Hepatitis B is a dangerous infectious disease which is one of the biggest causes of death in women. Indonesia is an endemic country for this disease, around 23 million Indonesian people have been infected with Hepatitis B. Specifically for Hepatitis B, Indonesia is one of the countries in the Southeast Asian region with highest prevalence rate. In this population, most of the transmission comes from the mother to child transmission route. The purpose of the literature review is to determine the factors that cause Hepatitis B in pregnant women.

Methods: The research design used in this study is to use the Literature review method. This technique is carried out with the aim of expressing various theories that are relevant to the problem being faced or being researched as reference material in the discussion of research results. In this study, the authors chose a quantitative research article with a cross sectional design or case control design with using scientific research from 2018 to 2023.

Results: The results showed that there is a relationship between parity (p=0.000), level of education (p=0.025), age at first marriage (p=0.007), frequency of spouse's marriage (p=0.008), sexual partner (p=0.031), spouses's hepatitis B status (p=0.001), history of spouse's mobility (p=0.007), family history of hepatitis B (p=001), health worker support (p=0.027), and history of needle use (p=0.013) with the incidence of hepatitis B in pregnant women.

Conclusions: Parity, level if education, age at first marriage, frequency of spouse's marriage, sexual partners, spouses's hepatitis B status, history of spouse's mobility, family history of hepatitis B, and health worker support are risk factors for the incidence of hepatitis B in pregnant women. Among all the risk factors found, sexual partners are the most risky factors for the incidence of hepatitis B in pregnant women in Indonesia.

LITERACY SOURCE

AUTHOR	YEAR	TITLE	RESULTS
Dwiana Kartika Putri, 1Rina Hanum,1Hotma Juliana Simanjuntak	2019	FACTORS AFFECTING PREGNANT WOMEN IN DO HEPATITIS EXAMINATION	tatistical test results obtained p-value = 0.017 and OR = 9.032 on knowledge variables. The value of p-value = 0.049 and OR = 8.288 on the husband's support variable. The value of p-value = 0.027 and OR = 11.039 on the variable of health worker support. Where p-value <α (0.05). Conclusions in the study there are factors (knowing, husband's support and health worker support) that affect pregnant women in conducting hepatitis examination in the Martoba Pematang Siantar Health Center Work Area in 2019.
Pratono1, Asri C. Adisasmita2	2019	RISK FACTORS FOR HEPATITIS B EVENTS IN PREGNANT WOMEN IN THE DKI JAKARTA REGION 2015 – 2016	Based on the results of multivariable analysis, it was found that pregnant women working in the non-formal field would tend to be protected 27% greater than Hepatitis B infection with OR = 0.73 (95% CI = 0.56 - 0.94). It was also found that pregnant women who had blood transfusions had a risk of 28.6 times greater risk of getting Hepatitis B with an OR = 28.62 (95% CI = 7.67 - 106.7). Pregnant women who have> 1 sex partner and who live at home with Hepatitis B patients at 21.4 and 20.4 times greater risk of getting Hepatitis B with OR = 21.47 (95% CI = 1.35 - 345.43) and OR = 20 (95% CI = 9.35 - 45)..
Putu Lusita Nati Indriani1, Helni Anggrain	2021	FACTORS AFFECTING THE OCCURRENCE OF HEPATITIS IN PREGNANT WOMEN	The results of the analysis of the relationship between age statistical tests showed p value = 1.0, parity with p = 0.142, and socio-economic with p = 0.12, it can be concluded that there is no relationship, and the results of research on the relationship between education and p = 0.02, occupation with p=0.001, sources of information with p=0.009, and the role of health workers with p=0.00; Based on the results of this study, there is a relationship between education, occupation, sources of information and the role of health workers with maternal knowledge about hepatitis B
Syifa Mustika, Dian Hasanah	2018	Prevalence of Hepatitis B Infection in Pregnant Women in Malang	Hepatitis B prevalence was obtained as much as 1% and 8% positive anti-HBs was found in patients with negative HBsAg.
Yanyan Mulyani*, Vaurel Nurul Salsabil	2020	Pengetahuan Dan Sikap Ibu Hamil Tentang Pencegahan Penularan Penyakit Hepatitis B Pada Janin Di Puskesmas Ciaparay Kabupaten Bandung Tahun 2019	Hasil dari penelitian ini adalah sebanyak 34 responden (53.1%) memiliki pengetahuan kurang. 19 responden (29.7%) memiliki pengetahuan cukup, dan 11 responden (17.2%) memiliki pengetahuan baik. Sedangkan 28 responden (43.8%) memiliki sikap negative, dan 36 responden (56.2%) memiliki sikap positif.
Margaretha Pither1*, Andi Yusuf2, Rahmawati Azizi3*	2021	Risk Factors for Hepatitis B Incidence in Pregnant Women in East Luwu District	The statistical test showed that the level of education (p-value = 0.027; OR = 2.705; 95% CI: 1.197-6.113), parity (p-value = 0.023; OR = 2.846; 95% CI: 1.228-6.697), and sexual partner (p-value = 0.031; OR = 9.333; 95% CI: 1.121-77.704) is a risk factor for hepatitis B incidence in pregnant women. Meanwhile, the age group (p-value = 0.177) and occupation (p-value = 0.059) were not risk factors for the incidence of hepatitis B in pregnant women.
Raina Khairana Denando1*, Widya Hary Cahyati	2022	RISK FACTORS OF HEPATITIS B IN PREGNANT WOMEN IN THE CITY OF SEMARANG, 2020-2021	he results showed that there is a relationship between parity (p=0.000), education level (p=0.025), age at first marriage (p=0.007), frequency of spouse's marriage (p=0.008), spouses's hepatitis B status (p=0.001), history of spouse's mobility (p=0.007), family history of hepatitis B (p=001), and history of needle use (p=0.013) with the incidence of hepatitis B in pregnant women.
Sukmawati, Endang Budiati, Nur Sefa Arief Hermawan, Aila Karyus, Kodrat Pramudho	2022	RISK FACTORS FOR HEPATITIS B VIRUS INFECTION IN PREGNANT WOMEN	The results of the study using the chi-square test obtained P-value 0.001 < 0.005, it can be said that there is a significant relationship between history of transfusion and hepatitis B. P-value is 0.000 < 0.005, so it can be said that there is a significant relationship between family history and hepatitis B. P-value 0.000 < 0.005, it can be said that there is a significant relationship between toothbrush use and Hepatitis B. P-value 0.000 < 0.005 means that there is a significant relationship between ANC and Hepatitis B. P- value 0.000 < 0.005 means that there is a significant relationship between shaving equipment.
Fiya Diniarti 1*), Tuti Rohani) 2 Wulandari Prasentya	2022	Determinant Factors of Hepatitis B Incidence On Pregnant Women	The description of hepatitis B cases in the Bengkulu City Region includes the Work Area of 20 Puskesmas with groups (51.4%) aged 16-40 years, some respondents (54.3%) with low education levels, some respondents (52.9%)) who have a family history. more than some (73.6%) had no history of immunization, more than some 80 respondents (57.1%) were multigravida. Bivariate analysis resultsThere is a relationship thatsignificant between ages(p value=0.004) OR=2.8; 95%CI=1.4 5.6,level of education(P value=0.004) OR=2.8; 95%CI=1.4-5.7,family history(P value=0.001) OR=3.6;95%CI=1.7-7.4, immunization history (P value=0.002) OR=3.7; 95%CI=1,6=8,5,gravida (p value=0,004) OR=2,9; 95%CI=1.4-5.8 with the incidence of Hepatitis B in Pregnant Women in the Bengkulu City Region in 2021.
Arina Nur Hidayah1, Wiwik Afridah2	2023	LITERATURE REVIEW: FAKTOR PENYEBAB HEPATITIS B PADA IBU HAMIL	The results of a literature review on the factors that cause Hepatitis B in pregnant women show that there are 2 out of 8 journals stating the factor of sexual partners, 3 out of 8 journals stated the history of injection needle use, 1 out of 8 journals stated the Hepatitis B vaccine history factor and 4 out of 8 journals stated the residence factor. The conclusion of this study is that sexual partners, history of injection needle use (blood transfusions), history of vaccines and living environment are factors causes of hepatitis B in pregnant women

Keywords: Risk factors, Hepatitis B, Pregnant women

PE-12

The Role of Mac-2 Binding Protein Glycosylation Isomer (M2BPGi) Level in Stratifying Hepatocellular Carcinoma (HCC) Risks in Chronic Hepatitis B (CHB) Patients with Oral Antiviral Therapy

Roland Helmizar[1], Nana Liana[2], Ruhsyahadati Ajisman[3], Rahma Triyana[4]

[1]Department of Internal Medicine, Faculty of Medicine Baiturrahmah University, Padang, Indonesia, [2]Department of Anatomic Pathology, Faculty of Medicine Baiturrahmah University, Padang, Indonesia, [3]Department of Clinical Microbiology, Faculty of Medicine Baiturrahmah University, Padang, Indonesia, [4]Department of Parasitology, Faculty of Medicine Baiturrahmah University, Padang, Indonesia

Aims: Mac-2 binding protein glycosylation isomer (M2BPGi) is a new glycol marker that has been developed for liver fibrosis detection. Its level has been shown predictive value for HCC development in CHB patients undergoing oral antiviral therapy.

Methods: A systematic search through Pubmed/MEDLINE, Scopus, Cochrane Library, and EBSCO was conducted to find studies about the role of M2BPGi level in stratifying HCC risks in CHB patients with oral antiviral therapy. The studies were selected and critically appraised. Data were then analyzed and summarized descriptively.

Results: A study by Tai-Chung Tseng et al. aimed to explore whether M2BPGi could be an HCC predictor in CHB patients receiving long-term entecavir therapy. The results showed that the M2BPGi level was positively associated with HCC development (the high M2BPGi group had an increased HCC risk compared to the low M2BPGi group, with a hazard ratio of 5.80 (95% CI 3.50-9.60)). Another study conducted by Yao-Chun Hsu et al. investigated the association between serum M2BPGi levels and the risk of HCC development after oral antiviral therapy in patients with CHB. The results showed that baseline M2BPGi levels were associated with HCC risk in multivariable Cox analysis, whereas levels at 1 or 2 years could not be predicted independently but showed good predictive performance at 3, 5, and 10 years. Another study by Lung-Yi Mak et al. showed that high serum M2BPGi levels at baseline were significantly associated with persistent advanced fibrosis or cirrhosis at 3 years despite long-term antiviral treatment and HCC development was observed in five patients during follow-up and was associated with a bigger median increase in the level of serum M2BPGi compared to patients without HCC (46% vs. 6.2%).

Conclusions: M2BPGi level can serve as an independent predictor of HCC development in CHB patients undergoing antiviral therapy. Higher M2BPGi levels are associated with increased HCC risk.

Keywords: Mac-2 Binding protein glycosylation isomer (M2BPGi), Hepatocellular carcinoma (HCC), Chronic hepatitis B (CHB), Oral antiviral therapy

PE-13

Superior Performance of Intrahepatic HBV Markers to Circulating Markers in Predicting Sustained Inactive Carriers in Chronically Infected Patients

Hye Seon Kim[2,3], Jin Seoub Kim[2,3], Ji Min Kim[2,3], Jung Hyun Kwon[1,2], Ji Won Han[1,2], Pil Soo Sung[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2*]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, [2]The Catholic University Liver Research Center, [3]Department of Biomedicine & Health Sciences, Graduate School, The Catholic University of Korea, Seoul

Aims: Although HBeAg seroconversion is regarded as a hallmark of clinical remission of chronic hepatitis B, a certain proportion of patients develop HBeAg-negative hepatitis (ENH) thereafter. Currently, no effective markers are readily available for discriminating ENH phases. Our study aimed to analyze blood and intracellular HBV markers to well predict sustained inactive status in HBeAg-negative patients.

Methods: A total of 81 antiviral-naïve patients [33 HBeAg-negative inactive carriers (IC), 20 Grey zone, and 28 patients with ENH] were recruited for the study and followed up for >12 months. After 12 months, IC were reclassified into sustained-IC and transition-IC (IC undergoing a transition to ENH) groups. We analyzed intrahepatic HBV markers, including covalently closed circular DNA (cccDNA), total HBV DNA, pregenomic RNA (pgRNA) by quantitative real-time PCR (qPCR) and compared them with serum HBV markers regarding their performance of predicting sustained-IC group versus transition group.

Results: At baseline, the IC group showed significantly lower intrahepatic cccDNA, total DNA and replicative efficiency (serum HBV DNA/cccDNA), virion productivity (rcDNA/cccDNA), serum HBV DNA, and HBV core-related antigen (HBcrAg) levels than the ENH group. During the 12 month-follow up, 10 (30.3%) of the 33 IC patients experienced a transition to ENH. cccDNA and cccDNA transcriptional activity (pgRNA) were significantly lower in sustained-IC group than transition group ($p<0.001$ and $p=0.046$, respectively) and showed superior performance in predicting sustained-IC (AUROC: 0.895 for cccDNA and 0.723 for transcriptional activity) compared to serum markers (0.688 for HBsAg; 0.675 for HBcrAg).

Conclusions: IC patients have a significantly decreased replicative activities of both intrahepatic and circulating HBV markers compared to ENH patients. Intracellular cccDNA show superior performance for discriminating sustained-IC from grey-zone or ENH in chronically infected HBeAg-negative patients.

Keywords: Hepatitis B virus, HBeAg-negative patients, CcDNAc, Inactive carrier

PE-14

Reduced Intrahepatic Levels and Transcriptional Activity of cccDNA Contribute to Lower Viremia in HBeAg-Negative Chronic Hepatitis B Patients

Hye Seon Kim[2,3], Jin Seoub Kim[2,3], Ji Min Kim[2,3], Jung Hyun Kwon[1,2], Ji Won Han[1,2], Pil Soo Sung[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2*]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, [2]The Catholic University Liver Research Center, [3]Department of Biomedicine & Health Sciences, Graduate School, The Catholic University of Korea, Seoul

Aims: Replicative and transcriptional activities of HBV vary with the natural immune phase of chronic hepatitis B (CHB) and still remain poorly understood. The aim of our study is to investigate the serum and intrahepatic markers of HBV replication according to HBeAg status among CHB patients.

Methods: A total of 111 patients, including 60 HBeAg-positive and 51 HBeAg-negative treatment-naive patients who underwent liver biopsy, were enrolled in our study. We measured intrahepatic HBV covalently closed circular DNA (cccDNA) and pregenomic RNA (pgRNA) by quantitative real-time PCR and quantified serum HBV DNA, HBsAg, and HBV core-related antigen (HBcrAg) levels in patients with elevated ALT levels (>40 IU/L).

Results: Serum HBV DNA, HBsAg, HBcrAg levels were higher in HBeAg-positive CHB patients than in HBeAg-negative CHB patients (7.3 vs 5.7 log IU/ml; 3.6 vs. 3.2 log IU/ml; 7.5 vs 5.4 log IU/ml, respectively). In HBeAg-positive CHB, intrahepatic cccDNA levels were 17.6-fold higher and pgRNA levels were 17.3-fold higher than in HBeAg-negative CHB. Intrahepatic total HBV DNA levels (tDNA) were also 28.8-fold higher in HBeAg-positive vs. HBeAg-negative CHB patients. Intrahepatic cccDNA and pgRNA levels showed a positive correlation with serum HBV DNA, HBsAg and HBcrAg levels in HBeAg-positive CHB patients, but the correlation disappeared in HBeAg-negative CHB patients.

Conclusions: HBeAg loss is associated with reduced intrahepatic cccDNA and transcriptional activity, which results in a decrease in HBV DNA and HBcrAg levels in patients with CHB. This finding suggests that HBeAg is an important determinant of HBV viral replication and that viremia and viral antigens fairly reflect intrahepatic cccDNA amounts, transcriptional and replicative activities in HBeAg-positive CHB, but not HBeAg-negative CHB.

Keywords: Hepatitis B virus, Intrahepatic cccDNA, HBeAg

PE-15

Correlation between Platelet-Lymphocyte Ratio and Degree of Liver Fibrosis in Chronic Hepatitis B Patients in Indonesia

Putri Ayu[1], Roland Helmizar[2], Rahmat Fauzan[3]

[1]Department of Economics, Andalas University, Indonesia, [2]Department of Internal Medicine, Baiturrahmah University, Indonseia, [3]Departement of Education, Padang State University, Indonesia

Aims: Liver fibrosis, a condition characterized by the scarring of the liver, can be caused by chronic liver inflammation, primarily resulting from the hepatitis B and C viruses. Assessing the degree of liver fibrosis is essential for determining the progression of the disease and providing timely and accurate treatment for patients with chronic hepatitis. One predictive factor for the incidence of liver fibrosis is the Platelet to Lymphocyte Ratio (PLR), which measures the ratio of platelets to lymphocytes in the blood. This study aims to investigate the relationship between PLR and liver fibrosis in patients with chronic hepatitis B in Indonesia.

Methods: This is a literature review study taken from reputable articles that discuss Platelet to Lymphocyte Ratio (PLR) with liver fibrosis in Indonesia. The method used is descriptive analysis.

Results: The correlation between Platelet to Lymphocyte Ratio (PLR) and liver fibrosis in hepatitis B patients was investigated in three study areas in Indonesia. The findings of a study conducted at Moewardi Hospital in Surakarta using cross-sectional data from January to July 2020, which involved 26 hepatitis B patients, revealed that the correlation test results indicated a correlation coefficient of r=-0.455 and p=0.020 between PLR and liver fibrosis values. Another research conducted at M. Djamil Padang Hospital between June 2020 and July 2021, involving 52 patients, demonstrated that the Spearman PLR correlation analysis showed a moderate positive correlation with fibroscan results (r=0.594; p<0.001). Furthermore, a study at Sanglah General Hospital between January 2016 and February 2017, comprising 52 patients, indicated a significant negative correlation between the severity of fibrosis in patients with CHB infection and PLR (r=-0.33; p=0.016).

Conclusions: The results revealed both positive and negative correlations between PLR and liver fibrosis. It was found that not all instances of PLR increase were associated with liver fibrosis. However, more than 50% (78 patients) of the total PLR exhibited a negative relationship with liver fibrosis in Chronic Hepatitis B patients in Indonesia.

Keywords: Platelet-lymphocyte ratio, Degree of liver fibrosis, Chronic hepatitis B, Indonesia

PE-16

Association of Hepatitis B Core Antibody with Treatment Response of Chronic Hepatitis B Patients

Putri Ayu[1], Roland Helmizar[2], Rahmat Fauzan[3]

[1]Department of Economics, Andalas University, Indonesia, [2]Department of Internal Medicine, Baiturrahmah University, Indonseia, [3]Departement of Education, Padang State University, Indonesia

Aims: Anti-HBc is one of the classical serological markers for HBV infection. This antibody istargeted to the core antigen of the hepatitis B virus (HBV) and is produced during active or previous HBV infection. We aimed to investigate the association of serum anti-HBc with treatment response of chronic hepatitis B (CHB) patients.

Methods: A systematic search through Pubmed/MEDLINE, Scopus, Cochrane Library, and EBSCO was conducted to find studies about the association of serum anti-HBc with treatment response of chronic hepatitis B (CHB) patients. The studies were selected and critically appraised. Data were then analyzed and summarized descriptively

Results: A study from Huang R et al. involved 281 patients in the immune clearance (IC) phase who were treated by nucleos(t)ide analogues (NAs) and followed for 48 weeks had anti-HBc data. Patients who had complete response (CR) after 48 weeks NAs treatment had significantly higher level of baseline anti-HBc as compare with patients who did not achieve CR (11.5 S/CO vs. 10.1 S/CO, p<0.001). Baseline anti-HBc was identified as an independent predictor for CR (OR 1.200, 95% CI 1.002-1.437; p<0.05). Another study from Dusheiko G et al. showed that the presence of anti-HBc has been as-

sociated with a higher risk of treatment failure, lower rates of hepatitis B surface antigen (HBsAg) seroconversion, and increased risk of disease reactivation after treatment discontinuation. The presence of anti-HBc, particularly when combined with other factors such as high viral load and low HBsAg levels, may indicate a more active HBV infection and a reduced likelihood of achieving sustained viral suppression.

Conclusions: Baseline anti-HBc level is a useful predictor of NAs therapy efficacy in HBeAg positive CHB patients. But, the association between anti-HBc and treatment response is an active area of research, and individual patient characteristics should be considered in clinical decision-making.

Keywords: Hepatitis B core antibody (Anti-HBc), Chronic hepatitis B, Efficacy, Treatment response

PE-17

Attenuation of Concanavalin A-Induced Autoimmune Hepatitis by Hesperidin in Mice via Gut Microbiota & Nrf2/NF-Kb Pathways Signalling Pathways

Deepika Singh[1], Manvendra SIngh[2]

[1]Department of Pharmaceutical Sciences, SHUATS, India, [2]Department of Computer Sciences, HMFA-MIET, India

Aims: Hesperidin (HP) has long been regarded as a traditional Indian medicine that treats skin conditions cirrhosis, rheumatoid arthritis pain, and cancer. Hesperidin is a viable drug candidate due to its low level of toxicity as well. The goal of this study was to examine the protective benefits of HP and its potential mechanisms using a mouse model of autoimmune hepatitis (AIH) induced by concanavalin A (Con A).

Methods: For 14 days prior to receiving Con A tail vein injections, mice were given various dosages of HP orally. The effects of HP were then assessed 12 hours after exposure to Con A on blood biochemical markers and liver histology. Western blotting, immunohistochemistry, and 16S rRNA sequencing were used to investigate the underlying processes of HP exposure and to identify changes in the gut microbiota and Nrf2 and NF-B signalling pathways.

Results: The serum levels of the cytokines tumour necrosis factor- and interleukin-6, as well as the pathological liver damage brought on by Con A, were all significantly reduced by HP pretreatment in a dose-dependent manner. Additionally, the multi-technique analysis's findings showed that HP activated the Nrf2 pathway, elevated the expression of the anti-oxidation components HO-1 and Nrf2, and downregulated the expression of Keap1. In addition, the NF-B signalling pathway was blocked. Unexpectedly, pre-treatment with HP greatly enhanced the gut microbiota's composition. This was probably due to the higher probiotic concentration. The Nrf2 and NF-B signalling pathways, as well as the gut microbiota, are thought to have a role in the hepatoprotective effect, according to our findings. Furthermore, pretreatment with HP may reduce the risk of AIH caused by Con A.

Conclusions: This study offers a theoretical foundation for the creation of HP as a powerful agent against Autoimmune hepatitis.

Keywords: Hesperidin, Hepatitis, Mice

PE-18

Evaluation and Comparative Study of Machine Learning-Based Models to Determine the Seropositivity of Hepatitis B Virus (HBV)

Deepika Singh[1], Manvendra Singh[2]

[1]SHUATS, [2]HMFA-MIET, India

Aims: Clinicians and public health experts struggle to identify patients who are at risk of contracting the hepatitis B virus. Traditional hepatitis screening methods can be more effective when used in conjunction with artificial intelligence and machine learning techniques, which can also be used to analyze big datasets and provide a complete picture of regional epidemiological profiles. In this research, four machine learning-based models for predicting the presence of hepatitis B were evaluated and their predictive abilities were compared.

Methods: Approaches Adults from the central region of India who experienced viral hepatitis screening in their primary care physicians' offices were evaluated as part of this prospective cohort screening study between March 2022 and October 2022. Four machine learning-based models, -naive bayes (NB), and random forest (RF) K nearest neighbors (KNN), support vector machine (SVM) were used, and their predictive abilities were evaluated, using the clinical characteristics of the patients that were taken from a structured poll.

Results: When used to forecast Hepatitis B virus status, all models that were tested outperformed each other. KNN algorithm had the best forecast performance (accuracy: 97.4%), followed by support vector machine and random forest, which both had 96.5% accuracy, and naive bayes, which had 94.3% accuracy. With accuracy levels varying from 77.3% to 95.46%, the predictive performance of these models for Hepatitis B virus status was modest.

Conclusions: The machine learning-based models might be helpful resources for predicting Hepatitis B Virus infection and risk stratification for adult patients who participate in a programme for viral hepatitis monitoring.

[Hepatitis B: Clinical Aspects]

PE-19

Epidemiology and Treatment Status of Hepatitis B Patients in a Korea HBV Cohort Study: A Prospective Multi-Center Cohort Study

ChangHee Chu[1], Jaehyun Seong[1], Oeuk Jeong[1], JeongGyu Lee[1], Jae Seung Lee[2], Jun Yong Park[2], Min Jin Go[1]

[1]Division of Clinical Research, Center for Emerging Virus Research, National Institute of Infectious Diseases, Korea National Institute of Health, Cheongju, Republic of Korea, [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: A systematic longitudinal cohort study is required to generate scientific evidence for interventions, treatments and intercept strat-

egies. In 2015, we established the Korea HBV Cohort Study which is a group study of five general hospitals, to investigate the antiviral treatment effects and clinical characteristics of hepatitis B patients in Korea. Each of the five hospitals was approved by the Institutional Review Board (IRB) to participate in the Korean HBV cohort study. Through this cohort, we are currently collecting the electronic case report form and biological samples.

Methods: This data included basic characteristic, risk factor, socio-demographic, clinical diagnosis, endoscope, medical imaging, biopsy, and serological test for HBV-infected patients. By 2022, 3,028 patients registered in this cohort, we analyzed epidemic status, clinical stage, and duration of progression to cancer. We performed the descriptive analysis and Kaplan-Meier analysis All statistical analysis was conducted using SAS 9.4.

Results: According to our inclusion criteria, a total of 2,398 patients were included. Males were 63.7%, and the average age was 52 years. 74.7% of patients are active hepatitis and 57.8% of them are HBeAg negative. Tenofovir (44.5%) and Entecavir (29.7%) were used for the treatment of hepatitis B. Family history (28.9%), smoking (37.0%), and drinking (46.0%) were analyzed the main risk factors. In this cohort, 35 patients developed liver cancer, and the average duration was 28.4 months. The incidence of cancer in patients with compensated cirrhosis (HBsAg+) was higher than other clinical stage (6.5%).

Conclusions: We reported the epidemic and treatment status of HBV-infected patients in a cohort study. Further studies are needed on basic, clinical and epidemiologic studies of disease progression. We are preparing the rules and regulation procedures to provide the cohort data or specimens to collaborators or scientists. Through these activities, we can conduct a national health care study on chronic infectious diseases.

Keywords: Hepatitis B, Cohort, Epidemiology, Korea

PE-20

Trends of Liver Function Tests among Residents Undergoing Health Screening in Beijing, 2009-2022

Yifan Geng[1], Bo Bi[1], Dehao Zhang[1], Xiaona Wang[2], Ye Tian[1], Yi Ning[1]

[1]Hainan Medical Univercity International School of Public Health and One Health, [2]MJ Healthcare Clinic, Beijing, P. R. China

Aims: This study aimed to investigate the trends of liver function of participants undergoing health screening in Beijing in a decade from 2009 to 2022.

Methods: From 26,260 participants in 2009 to 22,563 participants in 2022 attended health screening at MJ Healthcare during the period. A total of 449,270 person-time anonymised records of these participants were analyzed in this study. Results of five liver function tests were analyzed, including AST, ALT, GGT, ALP, and TBIL. Meta-regression was used to evaluate the long-term trends of each test result, adjusted for potential confounders including age, sex, Body Mass Index, fasting blood glucose, systolic blood pressure, and triglycerides. Subgroup analysis was performed by sex and age groups.

Results: The average age of the participants was 41.7±11.8 (Mean±SD) in 2009 to 43.4±11.5 in 2022. Fifty-four percent of them were male. After adjusting for the potential confounders, AST, ALT, and GGT showed statistically significant decreasing trends (P-value<0.01) during the period, while no significant trends was found for TBIL and ALP (P-values>0.05). In the subgroup analyses, the trends of AST, ALT, and GGT remained significant for both genders and three age groups of <30, 30-59 and >=60 years (P-values<0.01).

Conclusions: The study suggested a long-term decreasing trends in the three of five liver indicators (AST, ALT, and GGT) among physical examination participants in Beijing from 2009 to 2022. Expended Programme on Immunization with HBV vaccination probably be major contributor to the improved liver function during the decade. Other specific reasons for this trend possibly include improved lifestyle, medication use, and health technology.

Keywords: Lver function tests, Trends, Health screening, Beijing

PE-21

Predictors of Hepatitis Flare and Initiation of Antiviral Therapy in Nucleos(T)ide-Chronic Hepatitis B in Grey-Zone

Yunjeong Lee, Jihye Kim, Gwang Hyeon Choi, Eun Sun Jang, Sook-Hyang Jeong, Jin-Wook Kim

Department of Medicine, Seoul National University Bundang Hospital and Seoul National University College of Medicine

Aims: Chronic hepatitis B (CHB) patients without significant liver inflammation, i.e., immune-tolerant or HBeAg-negative inactive carrier phase, are followed without nucleos(t)ide analogs (NAs) until transaminase level elevates. A substantial number of patients show low/normal transaminase with persistent viremia, known as "grey zone" phase. It is unclear, however, which patients in grey zone have high probability of hepatitis-flare. This study aimed to investigate the clinical and laboratory characteristics which may predict the hepatitis flare and becoming initiated of antiviral therapy in nucleos(t)ide-naïve patients with low/normal transaminase level (both AST/ALT <80 U/L), along with HBV DNA levels >2,000IU/mL in HBeAg-negative and >20,000 IU/mL in HBeAg-positive CHB.

Methods: We reviewed nucleos(t)ide analogue-naïve, noncirrhotic CHB patients with low/normal transaminase level (both AST/ALT <80 U/L) seen at our hospital between April 2003 and April 2023. 467 HBeAg-positive patients with HBV DNA level >20,000 IU/mL and 2,008 HBeAg-negative patients with HBV DNA level >2,000 IU/mL were included in our analysis. The Cox regression model was used to identify the factors associated with initiation of antiviral therapy throughout the follow-up period in each group. Age, gender, serum AST, ALT, albumin, prothrombin time (INR), bilirubin, platelet counts, HBsAg level as well as the HBV DNA level were tested.

Results: In the HBeAg-negative CHB, lower serum albumin (hazard ratio [HR]=0.45, 95% confidence interval [CI]: 0.31–0.65, P value=0.00) and prolonged prothrombin time (HR=4.37, 95% CI: 1.40–13.61, P value=0.01) along with higher serum ALT and HBV DNA level were associated with the initiation of antiviral therapy. In contrast, there were no statistically significant independent factors associated with initiation of antiviral therapy other than higher baseline serum AST levels in HBeAg-positive CHB.

HBeAg (+)	Hazard Ratio	95% CI	P value
Age	1.00	0.99-1.01	0.75
Gender	1.06	0.78-1.45	0.70
Log HBsAg	0.89	0.62-1.29	0.55
Log HBV DNA	1.03	0.85-1.24	0.79
ALT	0.99	0.98-1.01	0.35
AST	1.02	1.00-1.04	0.03
Bilirubin	0.75	0.48-1.15	0.18
Albumin	0.66	0.42-1.03	0.07
PT (INR)	1.01	0.21-4.95	0.99
Platelet counts	1.00	1.00-1.00	0.56
HBeAg (-)	**Hazard Ratio**	**95% CI**	**P value**
Age	1.01	1.00-1.02	0.12
Gender	0.91	0.67-1.24	0.56
Log HBsAg	0.80	0.61-1.05	0.11
Log HBV DNA	1.47	1.30-1.66	0.00
ALT	1.01	1.00-1.03	0.04
AST	0.99	0.97-1.01	0.48
Bilirubin	0.86	0.56-1.32	0.48
Albumin	0.45	0.31-0.65	0.00
PT (INR)	4.37	1.40-13.61	0.01
Platelet counts	1.00	1.00-1.00	0.13

Conclusions: Decreased serum albumin level and prolonged prothrombin time along with high baseline HBV DNA levels were predictive of the hepatitis flare and initiation of NA therapy in HBeAg-negative grey zone CHB patients. In HBeAg-positive grey zone, only elevated baseline AST levels were associated with hepatitis flare.

Keywords: Chronic Hepatitis B, Nucleos(t)ide analogue, Antiviral therapy, Predictor

PE-22

Baseline and Reduction at 1 Year of Hepatitis B Surface Antigen Level Predicts Functional Cure and Low HBsAg Titer: A Long-Term Kinetics of Hepatitis B Surface Antigen according to Disease Status

Soon Kyu Lee[1,2], Jung Hyun Kwon[1,2*], Soon Woo Nam[1,2]

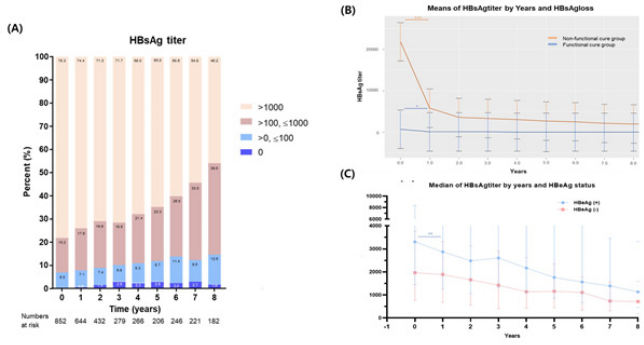
[1]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Long-term nucleos(t)ide analogue (NA) therapy is usually mandatory in patients with chronic hepatitis B (CHB) infection. In the stopping rule, a low HBsAg titer (<2log IU/mL) has been suggested as the cut-off level for stopping NA therapy. However, the long-term kinetics of quantitative HBsAg levels and their predictive role in functional cure or stopping NA strategy remain unclear.

Methods: We consecutively enrolled 1661 patients with chronic hepatitis or liver cirrhosis who started NA therapy between 2006 and 2020. Finally, 852 patients (entecavir, n=287; tenofovir, n=565), who were serially checked annually for HBsAg levels, were analyzed in our study. Patients were classified into three groups according to the quantitative HBsAg levels: the low HBsAg group (HBsAg <2log IU/mL), the intermediate HBsAg group (2log ≤ HBsAg <3log IU/mL), and the high HBsAg group (HBsAg ≥ 3log IU/mL). The primary outcome was the identification of the rate and predictive factors of functional cure and achievement of low HBsAg titer during NA treatment. Moreover, we also evaluated the long-term kinetics of HBsAg levels and the development of hepatocellular carcinoma (HCC).

Results: During a mean follow-up of 6.3±3.6 years, the rate of functional cure after NA treatments was 2.28% (n=19), and 108 patients (12.9%) achieved a low HBsAg group. The rate of the low HBsAg and intermediate group increase from 6.5% and 15.3% at baseline to 7.7% and 17.9% at the first year, and 14.2% and 39.6% at 8 years, respectively (Figure A). The changes in the mean levels of HBsAg showed a steep reduction in the first year of NA therapy than after the first year in both functional and non-functional cure groups (Figure B). The HBeAg (+) group demonstrated a higher baseline HBsAg titer and a greater reduction at one year compared to the HBeAg (-) group (Figure C). Among patients with HBeAg (+), the chronic hepatitis group showed a significant reduction at one year. In multivariate Cox-regression analysis, lower baseline HBsAg titer (<1000 IU/mL), and the presence of reduction in the 1 year of HBsAg titer were both identified as predictive factors for an achievement of functional cure and low HBsAg titer after NA therapy. During follow-up, there was no development of HCC in patients achieving functional cure.

Conclusions: Our study demonstrated the rapid reduction in HBsAg titer in the first year of NA therapy and an increase in low HBsAg group during NA therapy. Moreover, lower baseline HBsAg titer and a decrease in the first year of HBsAg titer may predict functional cure and low HBsAg titer during NA treatments.



Keywords: Nucleos(t)ide analogue, Hepatitis B, Functional cure, Hepatitis B surface antigen

PE-23

Long-Term Outcomes of HBeAg-Positive Grey-Zone Patients

Dongwoo Cho[1,2], Jung Hyun Kwon[1], Soon Kyu Lee[1], Soon Woo Nam[1], Jeong Won Jang[2]

[1]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: HBeAg-positive patients consisted of immune tolerant (IT) and immune active (IA) groups. Recently, a more detailed classifica-

tion beyond the original criteria of ALT levels or HBV DNA levels has placed these patients into a grey-zone (GZ). It remains unclear whether these patients will demonstrate different long-term outcomes from the conventional group.

Methods: Out of 256 HBeAg-positive IT and IA patients in a naive cohort from our hospital (published in year 2011) 201 without HCC were finally analyze. Currently, IT was strictly re-defined as HBV DNA >10^7 IU/mL and ALT<40 U/L, while IT-GZ was defined by HBV DNA >107 IU/mL and 40≤ALT<80 U/L. IA was defined as ALT >80 U/L regardless of HBV DNA levels, IA-GZ defined by HBV DNA <10^7 IU/mL and ALT <80 U/L. We evaluated the rate of de novo HCC development and cumulative rate of antiviral therapy (AVT) of IT versus IT-GZ, IA versus IA-GZ groups.

Results: Of the 59 original IT patients, 39 were in the strict IT group and 20 were in the IT-GZ group. Of the 142 original IA patients, 93 were in the IA group and 49 were in the IA-GZ group. Both GZ groups had significantly lower levels of HBsAg, HBeAg, HBV DNA levels and platelet levels than IT and IA patients (p<0.01). The IA-GZ group was older in the IA group. During a long-term follow-up period (9.1±4.4 year), 18 patients developed HCC (8 in IA, 10 in IA-GZ, and only 1 in IT-GZ). De novo HCC in IA-GZ group was slightly higher than in the IA group (p=0.040). At the baseline, starting rate of AVT in IA was higher in IA-GZ but de-novo AVT rate in IA-GZ was higher in IA. Finally, the cumulative rate of AVT was not significantly different between IT and IT-GZ, or IA and IA-GZ. In the IA group, de novo AVT or no AVT during follow-up compared to the starting AVT at baseline, was a significant risk factor (HR 4.747, p=0.035) for HCC development but not in the IA-GZ group (p=0.099). For the predicting the HCC in IA/IA-GZ group, male gender, HBeAg titer <200 IU/mL, HBV DNA <10^7 IU/mL, and ALT <80 U/L were significant variables.

Conclusions: The present study showed the long-term outcomes of IT and IA phase of HBeAg-positive patients including those in the GZ. In the re-defined phases, there was only one case of HCC development in IT-GZ group. The IA-GZ group had slightly higher HCC development than the IA group.

Keywords: Grey-zone, Hepatitis B virus, Hepatocellular carcinoma

PE-24

Discontinuation of Antiviral Therapy even after 12 Month-Maintenance Following Hematopoietic Stem Cell Transplantation Is Associated with the HBV Reactivation in HBsAg-Positive Subjects

Ji Won Han[1,2], Jeong Won Jang[1,2*], Pil Soo Sung[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul 06591, Republic of Korea

Aims: Hepatitis B virus (HBV) reactivation is a significant risk factor for HBsAg-positive patients undergoing hematopoietic stem cell transplantation (HSCT). Antiviral therapy (AVT) is crucial to prevent HBV reactivation; however, the duration of maintenance therapy after HSCT remains unclear.

Methods: This study included a historical cohort of 209 HBsAg-positive patients who received AVT before HSCT at Seoul St. Mary's Hospital between 2010 and 2020. HBV reactivation was defined according to the AASLD 2018 guideline. AVT was discontinued within 12 months after HSCT in 94 patients (45.0%, AVT<12 subgroup) and continued for over 12 months in 115 patients (55.0%, AVT≥12 subgroup). We determined the incidences and risk factors of HBV reactivation in these two subgroups and several subgroups.

Results: The AVT<12 subgroup had a significantly higher rate of HBV reactivation compared to the AVT≥12 subgroup (HR=6.4, p<0.001), and the cumulative reactivation rates at 24, 48, and 96 months after HSCT were 36.0%, 47.8%, and 58.3% in the AVT<12 subgroup, while 5.7%, 15.9%, and 31.1% in the AVT≥12 subgroup. Discontinuation of AVT at any time after HSCT (HR=13.7, p<0.001) and HBsAg quantification (qHBsAg) ≥ 41.8 IU/mL at HSCT (HR=11.5, p<0.001) were independent risk factors for HBV reactivation. In the AVT≥12 subgroup, the AVT stop (AVT≥12s) group (n=39) had a significantly higher rate of HBV reactivation compared to the AVT maintenance (AVT≥12m) group (n=76) (HR=6.6, p<0.001), and the cumulative reactivation rates at 24, 48, and 96 months were 24.6%, 42.1%, and 56.5% in the AVT≥12s group, and 3.6%, 3.6%, and 11.1% in the AVT≥12m group. High HBV DNA titer at HSCT ≥ 2,282 copies/mL (HR=2.8, p=0.025) and high qHBsAg at discontinuation ≥ 41.8 IU/mL (HR=9.6, p<0.001) were independent factors associated with HBV reactivation after AVT discontinuation. The cumulative incidences of HBV reactivation were 59.6%, 69.7%, and 74.8% at 12, 24, and 48 months following the discontinuation of AVT in the high qHBsAg subgroup (n=22), and 10.0%, 15.0%, and 15.0% in the low qHBsAg subgroup (n=24).

Conclusions: In HBsAg-positive patients undergoing HSCT, the risk of HBV reactivation is significantly associated with discontinuation of antiviral therapy even after 12 months of maintenance. Discontinuation of AVT may be considered with caution in patients with low qHBsAg titers during the follow-up period, regardless of the duration of AVT maintenance. Larger, prospective studies are needed to confirm these findings.

Keywords: Hepatitis B, Reactivation, Antiviral, Hematopoietic stem cell transplantation

PE-25

Aspirin Use and Risk of Hepatocellular Carcinoma and Gastrointestinal Bleeding in Patients with HBV-Related Cirrhosis

Mi Na Kim[1,2,3], Geun U Park[4], Jae Seung Lee[1,2,3], Hye Won Lee[1,2,3], Beom Kyung Kim[1,2,3], Seung Up Kim[1,2,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea, [4]Clinical and Translational Hepatology Laboratory, Seongnam, Republic of Korea

Aims: The use of aspirin in hepatocellular carcinoma (HCC) prevention is still uncertain in patients with hepatitis B virus (HBV)-related cirrhosis. In addition, results regarding whether the risk of gastrointestinal (GI) bleeding is associated with aspirin use in patients with

HBV related cirrhosis are controversial. Accordingly, we investigated the association between aspirin use and the risks of HCC and GI bleeding in HBV-related cirrhosis patients using a nationwide cohort.

Methods: We conducted a 3-year landmark analysis using nationwide cohort data from the National Health Insurance Service of South Korea. Patients with diagnosed with compensated HBV-related cirrhosis in 2005-2017 were included. Patients who were prescribed aspirin for at least 90 days consecutively during the 3-year exposure period were classified as the aspirin-treated group. A propensity-score matching analysis was applied to balance the aspirin-treated and untreated groups. Using Cox proportional hazard regression analysis, we estimated the risks of HCC and GI bleeding, accounting for competing events.

Results: A total of 12,687 patients (608 aspirin-treated and 12,079 untreated) were included in the analysis. During a median of 7.6 years of follow-up, HCC developed in 219 (36.0%) patients of the aspirin-treated group and 4,265 (35.3%) patients of the untreated group. After multivariate adjustment, the aspirin-treated group showed a significantly lower risk of HCC than the untreated group (adjusted hazard ratio [aHR]=0.84, 95% confidence interval [CI]=0.73-0.96; p=0.013). GI bleeding developed in 157 (25.8%) of the aspirin-treated group and 2,072 (17.2%) of the untreated group. The aspirin-treated group showed a significantly higher risk of GI bleeding than the untreated group (aHR=1.21, 95% CI=1.03-1.43; p=0.021). After propensity-score matching, the cumulative incidence rate of HCC was significantly lower in the aspirin-treated group than the untreated group (p=0.013, log-rank test). Whereas, the cumulative incidence rate of GI bleeding was significantly higher in the aspirin-treated group than the untreated group (p=0.025, log-rank test).

Conclusions: In patients with HBV-related cirrhosis, the aspirin-treated group showed a significantly lower risk of HCC than the untreated group, whereas the risk of GI bleeding was significantly higher in the aspirin-treated group.

Keywords: Aspirin, Hepatocellular carcinoma, Gastrointestinal bleeding, HBV-related cirrhosis

PE-26

Clinical Significance of Mac-2 Binding Protein Glycosylation Isomer in Korean Patients with Chronic Hepatitis B: Comparative Study of Non-Invasive Modality for Diagnosis of Liver Fibrosis

Jae-Sung Yoo[1], Hye Seon Kim[2], Jin Seoub Kim[2], Ji Min Kim[2], Ji Won Han[1], Pil Soo Sung[1], Si Hyun Bae[1], Jong Young Choi[1], Seung Kew Yoon[1], Jeong Won Jang[1*]

[1]Department of Internal Medicine, [2]Department of Biomedicine & Health Sciences, Graduate School, The Catholic University of Korea, Seoul, Korea

Aims: Mac-2 binding protein glycosylation isomer (M2BPGi), one of the novel, non-invasive fibrosis markers, has been evaluated for assessing liver fibrosis in a multitude of studies. Nevertheless, there is a scarcity of data on its diagnostic accuracy of M2BPGi for liver fibrosis in patients with chronic hepatitis B (CHB). The aim of this study is to investigate the clinical value of M2BPGi in assessing liver fibrosis in comparison with existing tools for liver fibrosis screening.

Methods: A total of 367 patients diagnosed with chronic hepatitis B between June 2016 and January 2022, at our liver units were entered in this study. Patients' medical records at the time of liver biopsy were retrospectively reviewed for determining M2BPGi, transient elastography (TE, FibroScan®), fibrosis-4 (FIB-4) index, and aspartate aminotransferase to platelet ratio index (APRI). Liver fibrosis on pathology was assessed based on METAVIR fibrosis scores.

Results: Pathological liver fibrosis grades of the 367 patients (216 males and 151 females; 163 without hemato-oncologic disease) were classified as F0 (n=59, 16%), F1 (n=84, 23%), F2 (n=40, 11%), F3 (n=68, 19%) and F4 (n=116, 32%). The median M2BPGi values for METAVIR fibrosis score F0, F1, F2, F3 and F4 were 1.9, 1.5, 1.4, 1.8, and 3.2 cutoff index (COI), respectively (p<0.001). M2BPGi levels weak correlated with the METAVIR scores (r=0.295, p<0.001). The area under receiver operating characteristic (AUROCs) with M2BPGi for ≥F2, ≥F3 and F4, were 0.6161, 0.6581 and 0.6908, respectively. To identifying significant fibrosis (F2-4), both M2BPGi and TE were significantly better than FIB-4 and APRI. The AUROCs with M2BPGi, TE, FIB-4, and APRI for diagnosing cirrhosis were 0.7208, 0.6908, 0.5051, and 0.6011, respectively. When analyzed without hemato-oncologic patients, the predictive value of M2BPGi for assessing liver fibrosis slightly increased (AUROC 0.6944 for significant fibrosis; 0.7837 for cirrhosis), which was significantly better than that of FIB-4 and APRI. With multivariate analysis with several other non-invasive fibrosis indices, M2BPGi didn't remain significant for diagnosing ≥F2, ≥F3, F4 (OR: 0.96, 95% CI: 0.77-1.20, p=0.7; OR: 1.05, 95% CI: 0.83-1.35, p=0.7; OR: 1.14, 95% CI: 0.93-1.44, p=0.060).

Conclusions: Serum M2BPGi together with TE is a reliable non-invasive tool for assessing liver fibrosis and better performs than FIB-4 and APRI. Its performance for assessing fibrosis appears to be more efficient among non-hemato-oncologic patients.

Keywords: Chronic hepatitis B, MPBPGi

PE-27

Clinical Usefulness of Serum ELF Levels on Diagnosing Liver Cirrhosis in Patients with Chronic Hepatitis B

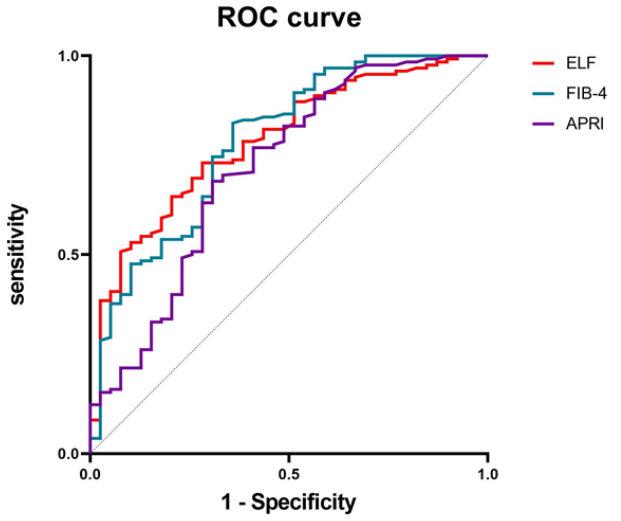
Jun Yeb Nam, Hyun Joon Park, Sang Uk Lee, Byung Cheol Yun, Kwang Il Seo, Jung Wook Lee

Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea

Aims: The Enhanced liver fibrosis (ELF) is known as a serological biomarker for predicting liver fibrosis. However, there was lack of data to use serum ELF level in Korean patients with chronic liver diseases including chronic hepatitis B (CHB). We aimed to assess its value for diagnosing liver cirrhosis (LC) in Korean patients with CHB.

Methods: We reviewed medical records for 169 patients with CHB who were performed serum ELF level in Kosin University Gospel Hospital from September 2020 to May 2022. Exclusion criteria were co-infection with chronic hepatitis C and significant alcohol intake. Multivariate logistic regression analysis was performed to identify independent predictors for diagnosing LC. The diagnostic accuracy of serum ELF for predicting LC was compared to that of other fibrosis markers, the fibrosis index based on four factors (FIB-4) and the

aspartate transaminase to platelet ratio index (APRI) using receiver operating characteristic (ROC).



ROC curve

Table 1. Baseline characteristics of study population

	Total (n=169)	Cirrhosis (n=130)	Non-Cirrhosis (n=39)	*P* value
Age, years[a]	62.3 (± 10.6)	63.7 (±8.9)	57.9 (±14.4)	0.003
Male sex[b]	128 (75.7)	103 (60.9)	25 (64.1)	0.053
Platelet count, $\times 10^9$/L[a]	143.4 (±68.4)	130.4 (±65.2)	186.6 (±61.2)	<0.001
Albumin, g/L[a]	3.7 (±0.7)	3.6 (±0.7)	4.1 (±0.7)	0.001
INR[a]	1.2 (±1.4)	1.3 (±0.6)	1.1 (±0.5)	0.182
Total bilirubin, μmol/L[a]	2.0 (±4.6)	2.4 (±5.2)	1.0 (±1.1)	0.1
r-GTP, U/L[a]	101.5 (±116.8)	109.6 (±124.4)	74.4 (±82.7)	0.099
AST, U/L[a]	79.9 (±106.1)	86.8 (±116.2)	56.7 (±56.8)	0.121
ALT, U/L[a]	67.3 (±177.4)	71.2 (±200.0)	54.0 (±55.7)	0.595
Creatinine[a]	1.1 (±1.4)	1.1 (±1.5)	1.0 (±0.9)	0.622
Sodium, mmol/L[a]	137.7 (±3.4)	137.5 (±3.5)	138.1 (±2.7)	0.374
ELF level[a]	10.9 (±1.5)	11.2 (±1.5)	9.8 (±1.2)	<0.001
FIB-4[a]	6.7 (±7.5)	7.7 (±8.0)	3.2 (±3.9)	0.001
APRI[a]	2.3 (±5.7)	2.8 (±6.4)	0.9 (±1.0)	0.079

Abbreviations: INR = international normalized ratio; r-GTP = r-glutamyltransferase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ELF= enhanced liver fibrosis; FIB-4 = fibrosis index based on four factors; APRI = aspartate aminotransferase-to-platelet ratio index
[a]Values are presented as mean (± standard deviation)
[b]Values are presented as number (%)

Results: The mean (±SD) of age of study patients was 62.3 (±10.6) years and the proportion of male was 75.7%. 130 (76.9%) patients were diagnosed with LC. The mean (±SD) of serum ELF level showed significant differences between LC group (11.2±1.5) and non-LC group (9.8±1.2) (p<0.001). (Table 1) Adjusting for age, gender, platelet count and albumin, serum ELF level was an independent predictor of LC [adjusted odds ratio (OR): 2.12, 95% confidence interval (CI) 1.46-3.07, p<0.001]. The area under the curve of serum ELF level for prediction of LC (0.786) was comparable to that of FIB-4 (0.786) and APRI (0.717), respectively. (p<0.001) (Fig. 1) The cut-off value of serum ELF that maximized the sum of sensitivity (73.1%) and specificity (71.8%) was 10.2.

Conclusions: Serum ELF level would be a reliable non-invasive marker for diagnosing LC in Korean patients with CHB.

Keywords: Enhanced liver fibrosis, Cirrhosis, Liver fibrosis, Chronic hepatitis B

PE-28

Hepatitis B Surface Antigen Seroclearance Rate in Cheorwon Area, Korea

Jae-Jun Shim, Kwon Kee Kim

Department of Internal Medicine, Cheorwon Hospital, Cheorwon, Republic of Korea

Aims: The seroclearance rate of hepatitis B surface antigen (HBsAg) is recognized to be very low, estimated at approximately 1% per year. With the significant improvement in life expectancy, there is a notable rise in the number of elderly patients with chronic hepatitis B. Nonetheless, there is a lack of study on the rates of HBsAg seroclearance especially in elderly patients.

Methods: The results of HBsAg tests from Jan. 2012 to May 2023 were extracted from the hospital electronic medical records. The testing for HBsAg was conducted using either qualitative or semi-quantitative methods.

Results: During 11 years, HBsAg testing was performed in 18,921 patients (male 46.4%, mean 51.2 years old). Overall HBsAg positive rate was 2.8% (N=534). A total of 137 patients had two or more HBsAg tests at least 6 months apart. During 658 person-years of follow-up, 26 patients showed HBsAg seronegative (3.95% / year). There was no difference in the seroclearance rates between men and women. The mean age of patients who achieved HBsAg seroclearance was 67.2 years, significantly higher than the 53.7 years of those who did not (p<0.001). There was a significant increase in the HBsAg seroclearance rate from age 60 years and older, with an annual clearance rate of 7.5%. Meanwhile, the rate was only 1.3% in the younger age groups (p<0.001).

Conclusions: HBsAg positive rate of the middle-age group is still high in Cheorwon area. Given the considerable rate of HBsAg seroclearance, it is crucial to obtain a comprehensive medical history of chronic hepatitis B and perform a high-sensitivity HBsAg test in patients over 60 years of age.

Keywords: Chronic hepatitis B, Epidemiology, Hepatitis B surface antigen

PE-29

A Mediation Analysis of Dynamic Process of Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients with Antiviral Treatment

Minjoo Cho[1], Yeojin Lee[1], Hyeyeon Hong[2], Jiwon Yang[2], Sung Won Chung[2], Won-Mook Choi[2], Danbi Lee[2], Ju Hyun Shim[2], Kang Mo Kim[2], Young-Suk Lim[2], Han Chu Lee[2], Seungbong Han[3] Jonggi Choi[2]

[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea

Aims: Antiviral treatment in chronic hepatitis B (CHB) patients without cirrhosis is determined by ALT levels and HBV DNA levels to prevent disease progression. We performed a mediation analysis to

examine the dynamic process of hepatocellular carcinoma (HCC) development in CHB patients treated with antiviral treatment.

Methods: A total of 4,832 patients with CHB who received with entecavir or tenofovir disoproxil fumarate at Asan Medical Center, Seoul, Korea were analyzed retrospectively. The association between HBV DNA levels and the on-treatment ALT normalization or Virological response (VR) were analyzed by multiple logistic regression. A mediation analysis was conducted to see whether these on-treatment ALT normalization or VR mediate the association between the pre-treatment HBV DNA levels and the HCC risk.

Results: The mean age was 48.3 years, and 62.0% were men. HBeAg was positive in 59.3% and cirrhosis was present in the 52.5% of the patients. On-treatment ALT normalization was achieved in 4,635 (95.9%) patients during the study period. At 1 year of antiviral treatment, patients with pre-treatment HBV DNA levels ≥ 8 log10 IU/mL showed the highest rate of on-treatment ALT normalization (81.8%), whereas those with pre-treatment HBV DNA levels of 6.0-6.99 log IU/mL showed the lowest rate of on-treatment ALT normalization (69.9%). A total of 4,511(93.4%) achieved VR during the overall treatment period. The rate of VR at 1 year of antiviral treatment was proportionally increased as the pre-treatment serum HBV DNA level decreases. HCC occurred in 455 patients with an annual incidence of 1.61/100 person-years. Pre-treatment HBV DNA levels of 6.0-6.99 (adjusted hazard ratio: 2.08, 95% CI: 1.43–3.04, p<0.001) showed the highest risk of HCC development after adjusting for confounders. Indirect effect of the 6.00–6.99 log IU/mL HBV DNA group or the HBV DNA group (<5 log IU/mL) through the on-treatment ALT normalization were statistically significant, which was smaller than direct effect. This indicates that indirect mediation effect of on-treatment ALT normalization on the risk of HCC is negligible. Regarding the association between the pre-treatment HBV DNA level, VR, and the HCC risk, indirect and direct effect of the pre-treatment HBV DNA groups through the VR were also negligible.

Conclusions: The present study demonstrated three important aspects; 1) CHB patients with pre-treatment serum HBV DNA levels of 6-7 had the highest risk of HCC development. 2) this group of patients showed the lowest rate of on-treatment ALT normalization at 1 year of antiviral treatment. 3) the risk of HCC development in patients with CHB was mainly determined by the pre-treatment serum HBV DNA levels rather than achievement of intermediate outcomes by antiviral treatment.

Keywords: Chronic hepatitis B, Antiviral treatment, ALT normalization, Virological response

PE-30

Impact of Metabolic-Associated Fatty Liver Disease on Treatment Response in Nucleos(t)ide Analogue-Treated Chronic Hepatitis B

Juseok Lee, Byung Seok Kim, Chang Hyeong Lee, Jeong Eun Song

Department of Internal Medicine, Daegu Catholic University School of Medicine

Aims: The impact of metabolic-associated fatty liver disease (MAFLD) on treatment response following nucleos(t)ide analogue (NA) treatment for chronic hepatitis B (CHB) patients has not been clearly elucidated. The aim of this study is to investigate the impact of MAFLD on complete viral response (CVR) and biochemical response in CHB patients who received NA treatment.

Methods: We retrospectively recruited CHB patients receiving NA therapy from 2014 to 2018. All patients were divided into CHB group and CHB with MAFLD group according to MAFLD diagnostic criteria. Therapeutic response related data were recorded and compared at multiple time points. Kaplan-Meier and Cox regression analyses were utilized to estimate the impact of MAFLD on complete virological response (CVR).

Results: A total of 235 patients were enrolled (183 CHB; 52 CHB with MAFLD). The majority of patients were male (58.5%) and HBeAg-positive (55.6%). MAFLD patients compared to non-MAFLD have more likely HBeAg-positive (73.1% vs 50.5%, p=0.004), hypercholesterolemia (38.5% vs 12.6%, p<0.001) and higher mean BMI (23.2±3.4 vs 26.3±4.5 kg/m^2, p<.001). Both groups achieved similar rates of CVR (88.5% vs 94.5%, p=0.128), ALT normalization (75.0% vs 85.7%, p=0.067), and HBeAg seroclearacne (15.8% vs 18.5%, p=0.715) during the follow-up of up to 65 months. but MAFLD group had lower cumulative rates of CVR at week 96, compared with non-MAFLD patients (79.8% vs 91.8%, p=0.003). In multivariate analyses, NAFLD was not independently associated with CVR outcomes, but lower baseline HBV DNA was positively associated with achieving CVR.

Conclusions: Concomitant MAFLD had no impact on the long-term rates of CVS in treated CHB patients.

Keywords: MAFLD, CHB, Virological response

PE-31

Efficacy of Antiviral Prophylaxis up to 6 or 12 Months after Completion of Rituximab in Resolved Hepatitis B: A Multicenter Randomized Controlled Trial

Heejoon Jang[1,2], Su Jong Yu[2], Hong-Ghi Lee[3], Tae Min Kim[4], Yun Bin Lee[2], Eun Ju Cho[2], Jeong-Hoon Lee[2], Jung-Hwan Yoon[2], Yoon Jun Kim[2]

[1]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea, [2]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Division of Hematology-Oncology, Department of Internal Medicine, Konkuk University Medical Center, Seoul, Republic of Korea, [4]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

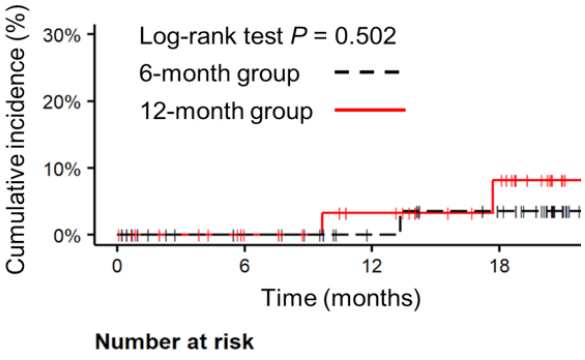
Aims: Rituximab occasionally induces reactivation of hepatitis B virus (HBV) in patients with resolved HBV, at times with fatal consequences. The optimal duration of prophylactic antiviral therapy in this situation is unclear. We aimed to investigate the difference in HBV reactivation according to the duration of prophylactic tenofovir disoproxil fumarate (TDF) in patients with resolved HBV and receiving rituximab.

Methods: A multicenter, randomized, open-label, prospective study was conducted in HBsAg-negative and anti-HBc-positive non-Hodgkin's lymphoma patients treated with rituximab-based chemotherapy. A total of 90 patients were randomized and received prophylactic TDF from the initiation of rituximab until 6 months (the 6-month

group) or 12 months (the 12-month group) after the completion of rituximab. The primary outcome was the difference in HBV reactivation and the secondary outcomes were the difference in hepatitis flare and adverse events between the two groups.

Results: In an intention to treat (ITT) analysis, HBV reactivation occurred in 1 of 43 patients (2.3%; 95% CI, 0.41%–12%) at a median of 13.3 months in the 6-month group and 2 of 41 patients (4.9%; 95% CI, 1.4%–16%) at a median of 13.7 months in the 12-month group. In a per protocol (PP) analysis, HBV reactivation occurred in 1 of 18 patients (5.6%; 95% CI, 0.99%–26%) at 13.3 months in the 6-month group and 1 of 13 patients (7.7%; 95% CI, 1.4%–33%) at 9.7 months in the 12-month group. The cumulative incidence of HBV reactivation was not significantly different between the two groups in ITT and PP analyses (p=0.502 and 0.795, respectively). The occurrence of adverse events was not significantly different between the two groups in ITT (9.3% in the 6-month group, 22.0% in the 12-month group, p=0.193) and PP analyses (5.6% in the 6-month group, 7.7% in the 12-month group, p>0.999).

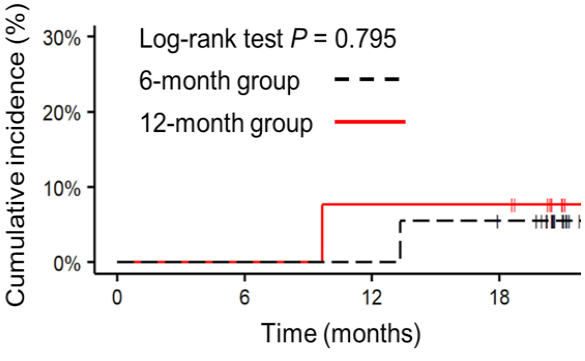
A



Number at risk

6-month group	43	35	28	22
12-month group	41	32	27	19

B



Number at risk

6-month group	18	18	18	16
12-month group	13	13	12	12

Conclusions: Prophylactic TDF up to 6 months after completion of rituximab-based chemotherapy is sufficient in terms of the efficacy and safety of reducing HBV reactivation in patients with resolved HBV.

Keywords: Hepatiti B, Resolved, Tenocore, Prophylaxis

PE-32

Entecavir versus Tenofovir on the Recurrence of Hepatitis B Virus Related Hepatocellular Carcinoma after Liver Transplantation: A Korean Nation-Wide Study

Deok-Gie Kim, Eun-Ki Min, Seung Hyuk Yim, Mun Chae Choi, Hwa-Hee Koh, Minyu Kang, Jae Geun Lee, Myoung Soo Kim, Dong Jin Joo

Department of Surgery, The Research Institute for Transplantation, Yonsei University College of Medicine, Seoul, South Korea

Aims: Tenofovir disoproxil fumarate (TDF) has been reported as having more potent anti-tumor effect than entecavir (ETV) in patients with chronic hepatitis B virus (HBV) infection, although there was discrepancy among studies. However, comparison of the two drugs regarding hepatocellular carcinoma (HCC) recurrence has not yet been evaluated in LT recipients.

Methods: We performed multicentric observational study using data of patients who underwent liver transplantation for HBV-related HCC. Patients were divided into two groups according to the type of oral nucleos(t)ide as an anti-HBV prophylaxis the; ETV (n=393) and the TDF group (n=452). Five-year outcomes were compared in the original cohort as well as using inverse probability treatment weight method followed by analyses with various Cox models.

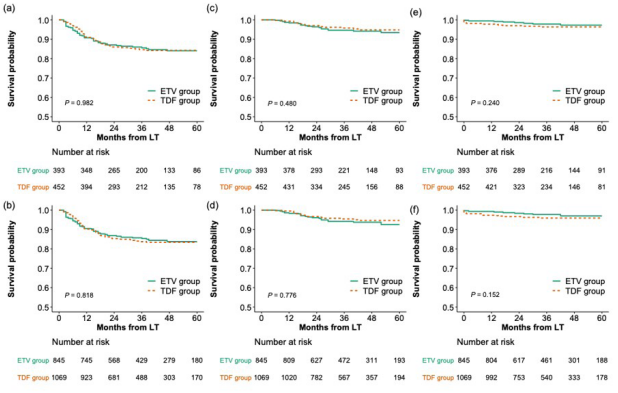


Figure 2. Kaplan-Meier curve analyses comparing ETV and TDF group.
(a) and (b), HCC recurrence free survival before and after IPTW, (c) and (d), overall survival before and after IPTW, (e) and (f), HBV recurrence free survival before and after IPTW

Results: In the original cohort, HCC-recurrence free survival (84.1% for the ETV group vs. 84.2% for the TDF group, p=0.982), overall survival (93.5% vs. 94.9%, p=0.480), and HBV-recurrence free survival (97.3% vs. 96.4%, p=0.240) were similar between the ETV and the TDF groups. IPTW analyses showed similar trend in all outcomes. In various Cox models such as covariate adjusted, propensity-score weighted, center effect adjusted, competing risk regression, and time dependent covariates adjusted models, ETV or TDF did not showed significant association with HCC recurrence and overall death. In various subgroups categorized by factors associated with HCC burden, such as Milan, Up-to-7, French risk score, pretransplant loco-re-

gional treatment, and salvage LT, ETV or TDF were not related with HCC recurrence or overall death.

Conclusions: In LT recipients from HBV-related HCC, neither ETV nor TDF showed significant superiority over HCC recurrence and overall death.

Keywords: Hepatitis B, Liver transplantation, Entecavir, Tenofovir disoproxil fumarate

PE-33

Treated Chronic Hepatitis B Is a Good Prognostic Factor of Diffuse Large B-Cell Lymphoma

Jeayeon Park[1†], Sung Won Chung[1†], Yun Bin Lee[1†], Hyunjae Shin[1], Moon Haeng Hur[1], Heejin Cho[1], Min Kyung Park[1], Jeonghwan Youk[2], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Tae Min Kim[2*], Jeong-Hoon Lee[1*]

[†]These three authors equally contributed as co-first authors.
* These two authors equally contributed as co-corresponding authors

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul, South Korea, [2]Department of Internal Medicine and Cancer Research Institute, Seoul National University Hospital, Seoul, South Korea

Aims: Chronic hepatitis B (CHB) is a risk factor for non-Hodgkin lymphoma (NHL) development. Our recent study suggested that antiviral treatment may reduce the incidence of NHL risk in CHB patients. This study compared the prognoses of hepatitis B virus (HBV)-associated diffuse large B-cell lymphoma (DLBCL) patients receiving antiviral treatment and HBV-unassociated DLBCL patients.

Methods: This study comprised 609 DLBCL patients who were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). All patients with CHB received antiviral treatment. Time to progression (TTP) and overall survival (OS) were the primary and secondary endpoints, respectively.

Results: A total of 609 patients were included in this study: 67 patients were HBsAg-positive (the CHB group) and 542 were HBsAg-negative (the non-CHB group). The median follow-up time was 48.5 (interquartile range=26.8–63.7) months. After balancing baseline characteristics with inverse probability of treatment weighting (IPTW), the CHB group was associated with longer TTP (hazard ratio [HR]=0.51, 95% confidence interval [CI]=0.29–0.92, log-rank p=0.03) than the non-CHB group. Similar results were obtained in multivariable analysis after IPTW (adjusted HR=0.49, 95% CI=0.27–0.91, p=0.02). The non-CHB group had shorter OS than the CHB group (HR=0.62, 95% CI=0.35–1.12, p=0.07), although the difference failed to reach statistical significance. The CHB group had no HBV reactivation flares, however two patients in this group died one of hepatocellular carcinoma and one of acute liver failure.

Conclusions: Our findings indicate that HBV-associated DLBCL patients receiving antiviral treatment have a significantly longer TTP than HBV-unassociated DLBCL patients after R-CHOP treatment.

Keywords: HBV, Non-Hodgkin lymphoma, Rituximab, Chemotherapy, Antiviral prophylaxis, Survival

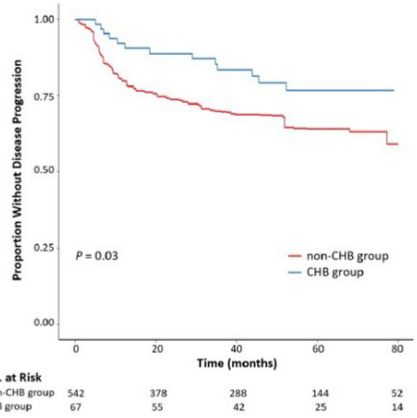


Figure. Kaplan–Meier estimates of DLBCL time to progression according to HBV infection after IPTW. Propensity score of IPTW were computed using age, sex, Ann Arbor classification, IPI risk, GCB subtype, LDH, presence of an extranodal lesion, bone marrow involvement, and cirrhosis.

Abbreviations: CHB, chronic hepatitis B; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; HBV, hepatitis B virus; IPI, International Prognostic Index; IPTW, inverse probability of treatment weighting; LDH, lactate dehydrogenase.

PE-34

COVID-19 Vaccination Alters NK Cell Dynamics and Transiently Reduces HBsAg Titers among Patients with Chronic Hepatitis B

Hyunjae Shin[1,*], Ha Seok Lee[2,*], Ji Yun Noh[3], June-Young Koh[2], So-Young Kim[2], Jeayeon Park[1], Sung Won Chung[1], Moon Haeng Hur[1], Min Kyung Park[1], Yun Bin Lee[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jae-Hoon Ko[4], Kyong Ran Peck[4], Joon Young Song[3], Eui-Cheol Shin[2,5,†], Jeong-Hoon Lee[1,†]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea; [3]Division of Infectious Diseases, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [4]Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]The Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science, Daejeon, Republic of Korea

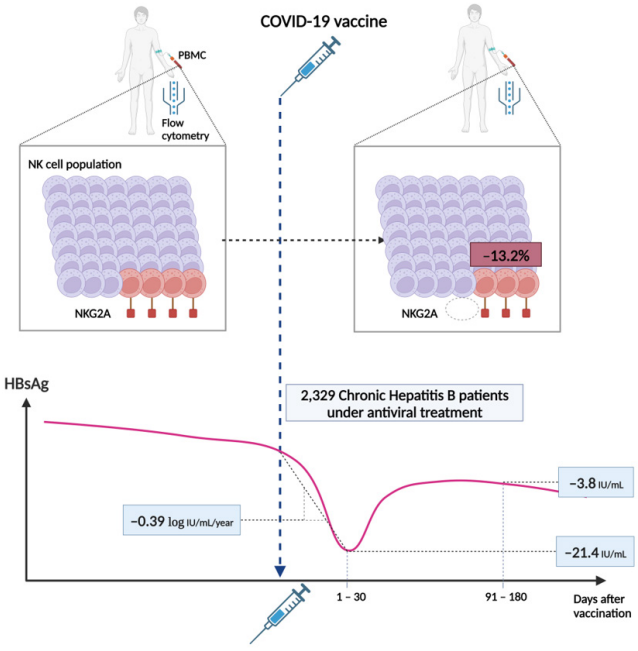
Aims: COVID-19 vaccination may non-specifically alter the host immune system. This study aimed to evaluate the effect of COVID-19 vaccination on HBsAg titer and host immunity in chronic hepatitis B (CHB) patients.

Methods: Consecutive 2,797 CHB patients who had serial HBsAg measurements during antiviral treatment were included in this study. Changes in the HBsAg levels after COVID-19 vaccination were analyzed. The dynamics of natural killer (NK) cells following COVID-19 vaccination were also examined using serial blood samples collected prospectively from 25 healthy volunteers.

Results: Vaccinated CHB patients (n=2,329) had significantly lower

HBsAg levels 1–30 days post-vaccination compared to baseline (median, -21.4 IU/mL from baseline), but the levels reverted to baseline by 91–180 days (median, -3.8 IU/mL). The velocity of the HBsAg decline was transiently accelerated within 30 days after vaccination (median velocity: -0.06, -0.39, and -0.04 log10 IU/mL/year in pre-vaccination period, days 1–30, and days 31–90, respectively). In contrast, unvaccinated patients (n=468) had no change in HBsAg levels. Flow cytometric analysis showed that the frequency of NK cells expressing NKG2A, an NK inhibitory receptor, significantly decreased within 7 days after the first dose of COVID-19 vaccine (median, -13.1% from baseline; p<0.001). The decrease in the frequency of NKG2A+ NK cells was observed in the CD56dimCD16+ NK cell population regardless of type of COVID-19 vaccine.

Conclusions: COVID-19 vaccination leads to a rapid, transient decline in HBsAg titer, which may be attributed to a decrease in the frequency of NKG2A+ NK cells.



Keywords: COVID-19 vaccine, NK cell, HBsAg, NKG2A

PE-35

Effect of Age on HBsAg Clearance in Children with HBeAg-Positive Chronic Hepatitis B Undergoing Antiviral Therapy

SukJin Hong[1], Byung-Ho Choe[2]

[1]Department of Pediatrics, School of Medicine, Daegu Catholic University, Korea, [2]Department of Pediatrics, School of Medicine, Kyungpook National University, Korea

Aims: This study aimed to identify the characteristics of children with HBeAg-positive chronic hepatitis B who achieved clearance of hepatitis B surface antigens (HBsAg) through antiviral treatment.

Methods: A total of 189 children with chronic hepatitis B were treated with anti-hepatitis B virus (HBV) medication, including Lamivudine, Adefovir dipivoxil, Entecavir, and Tenofovir disoproxil fumarate. The treatment group comprised patients who had been HBsAg positive for at least 6 months, with a continuous increase in ALT levels to more than twice the normal upper limit for at least 3 months without any other cause, or confirmed through liver tissue examination. Treatment was continued if ALT levels normalized and HBV DNA was undetectable, until HBeAg seroconversion occurred, followed by an additional 1-2 years of treatment. Subsequently, patients were followed up to assess the clearance of serum HBsAg. We confirmed the loss of HBsAg using quantitative hepatitis B surface antigen testing. Patients with e antigen-negative chronic hepatitis B, spontaneous e antigen seroconversion, or concomitant hepatitis from other causes were excluded. Various clinical variables were compared between patients who achieved HBsAg clearance and those who did not, including age, pretreatment serum levels of ALT and HBV DNA, treatment duration, time to ALT normalization, HBV DNA negativization, HBeAg seroconversion, and HBsAg clearance.

Results: HBsAg clearance was observed in 34 out of 189 (18%) patients. The mean time from initiation of antiviral treatment to total HBsAg clearance was 30.6±38.7 months (mean±SD; range: 1-204 months). Only the age at which treatment was initiated showed a significant association with HBsAg clearance. Children who achieved HBsAg clearance were significantly younger than those who did not (median [interquartile range]: 2.6 [1.3-5.8] years vs 9.8 [5.1-13] years, respectively; p<0.0001). Furthermore, when comparing the proportion of patients with HBsAg loss based on the age of 6, a significantly higher proportion was observed in those under 6 years old (49.0% vs 12.1%; p<0.0001). All 34 of these patients eventually developed antibodies to HBsAg.

Conclusions: Children in early childhood, particularly those under the age of 6, have a higher likelihood of HBsAg clearance compared to older children when treated for HBeAg-positive chronic hepatitis B with anti-HBV medication.

Keywords: Hepatitis B surface antigens, Hepatitis B e antigens, Seroconversion, Antiviral agents, Children

[Hepatitis B: Current Treatment]

PE-36

Bibliometric Study on Antiviral Agents against Hepatitis B Virus in Scopus Database (2018-2023)

Rian Ka Praja[1], Reny Rosalina[2]

[1]Department of Microbiology, Faculty of Medicine, Universitas Palangka Raya, Central Kalimantan, Indonesia, [2]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Palangka Raya, Central Kalimantan, Indonesia

Aims: The hepatotropic hepatitis B virus (HBV) is capable of causing immunological anergy in humans, where it can cause a chronic and persistent infection. Currently, available treatments for HBV infection include immunomodulators like interferon therapy as well as antiviral drugs that directly target viral replication. The goal of the current study was to provide insights into the results of international research on antiviral drugs against HBV.

Methods: A bibliometric analysis was done using the Scopus database for the period from 2018 to 2023. VOSviewer software version 1.6.19 was employed to conduct co-authorship and co-occurrence analyses.

Results: The search strategy used identified 2,717 papers in the Scopus database from 2018-2023. Specifically, from 2018 to 2022, research papers related to antiviral drugs against HBV totaled around 400 - 500 papers per year. In 2023, as of May, there have been 173 publications on antiviral drugs for HBV. China was the most active country in publishing research papers on anti-HBV agents with 985 documents. The research institution of Capital Medical University, China had the highest number of publications with 185 papers. The top five frequent keywords related to antiviral agents against HBV were entecavir, tenofovir, lamivudine, telbivudine, and adefovir. Journal of Viral Hepatitis was considered the most productive journal publishing papers on antiviral agents for HBV treatment.

Conclusions: The hard work of scientists from various countries has succeeded in finding various antiviral agents that have the potential to treat HBV infection. In addition, research related to the discovery of novel antiviral agents that are safer and more effective for HBV infection is still a challenge as well as an interesting topic in the medical field.

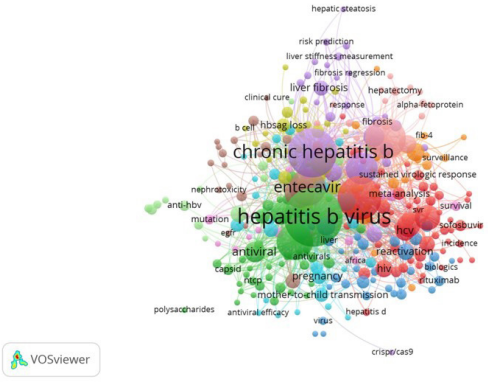


Figure 1. Network visualization map of most frequent terms in author's keywords of the retrieved papers on antiviral agents against HBV in the Scopus database (2018-2023)

Table 1. Top ten active countries publishing papers on antiviral agents against HBV in the Scopus database (2018-2023)

No.	Country	Document	Citations	Total link strength
1	China	985	8829	501
2	United States	529	11202	779
3	South Korea	251	3725	303
4	Taiwan	251	3382	303
5	Japan	185	2457	254
6	Italy	140	2758	268
7	France	137	3301	299
8	Germany	136	3055	398
9	United Kingdom	126	2375	350
10	Canada	119	2381	294

Keywords: Antiviral agents, Bibliometric study, Hepatitis B virus (HBV), Viral replication

PE-37

Efficacy Comparison of High Genetic Barrier Nucleos(t)ide Analogues in Treatment-Naïve Chronic Cepatitis B Patients: A Network Meta-Analysis

Jaejun Lee[1,2#], Ahlim Lee[3,4#], Pil Soo Sung[3,6], Jeong Won Jang[3,6], Si Hyun Bae[3,4], Jong Young Choi[3,6], Seung Kew Yoon[3,6], Hyun Yang[3,4*]

[1]The Catholic University Liver Research Center, Department of Biomedical Science, The Graduates School of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Armed Forces Goyang Hospital, Goyang, Republic of Korea, [3]The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul 03383, Republic of Korea, [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, 07345, Republic of Korea, [6]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, 06591, Republic of Korea

Aims: Chronic HBV infection is major cause of liver fibrosis and cirrhosis which then develops hepatocellular carcinoma (HCC). Four high genetic barrier nucleos(t)ide analogues (NA) for chronic hepatitis B, namely entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and besifovir dipivoxil maleate (BSV) have been established. However, there are only a few study comparing these four drugs. The aim of this study is to investigate the efficacy of four high genetic barrier NAs using a network meta-analysis of randomized trials and propensity score matched cohorts.

Methods: Systematic search was performed using PubMed, Cochran library, and EMBASE and included randomized controlled trials and cohort studies performed with propensity score matching method. Studies on treatment-naïve chronic hepatitis B patients treated with ETV, TDF, TAF, or BSV were included. Outcomes included ALT normalization and HBeAg seroclearance at week 48 and undetectable HBV DNA at week 48 and 96. ROB2.0 and ROBANS-I were used for quality assessment of included studies. Network meta-analysis was performed to synthesize the results.

Results: In total, 15,000 patients from 16 studies were included. In terms of 48- and 96-week virologic response, TDF outperformed ETV with statistical significance (48 week: odds ratio 1.38, $p<0.001$; 96 week: odds ratio 1.57, $p=0.004$). ETV was ranked first for 48-week biochemical response and outperformed TDF (odds ratio 0.76, $p=0.028$). In the sensitivity analyses, 48-week virologic responses from randomized-controlled trials were compiled, and the same trend toward the superiority of TDF over ETV was found (odds ratio=1.51, $p=0.030$).

Conclusions: Four high genetic barrier NAs have been compared and TDF and TAF were more likely to achieve 48 week virologic response and ETV was better at achieving 48 week biochemical response. Additional studies with longer treatment duration and large-sample studies are mandatory to determine the benefit of each drugs.

Keywords: Besifovir, Virologic response, Biochemical response, High-genetic barrier NUCs

PE-38

Severe Extrahepatic Manifestation Involving Mucosa and Skin in Chronic Hepatitis B Infection: A Case Report

Shin Young Park[1], Su Hyeon Cho[1], Nah Im Kim[2], Sung Kyu Choi[1], Jae Hyun Yoon[1]

[1]Department of Gastroenterology and Hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea, [2]Deparment of Pathology, Chonnam National University Hospital and Medical School, Gwangju, South Korea

Aims: HBV is a hepatotropic virus primarily causing inflammation in the liver, and it exhibits a wide range of clinical courses, from asymptomatic to fulminant hepatitis. However, in some cases, extra-hepatic localized or systemic inflammatory reactions associated with Hepatitis B virus (HBV) infection and activity have been reported.

Methods: Here, we would like to report on one case of HBV flare in which there was atypical extra-hepatic manifestation confined to the skin and mucosal involvement despite NUC treatment.

Results: A 53-year-old woman with chronic hepatitis B (CHB) in the immune tolerant phase presented with jaundice and nausea. She had no other comorbidities, and her liver function tests were improving after antiviral treatement, but a skin rash and mucosal inflammation such as conjunctivitis and dry mouth were observed, which gradually worsened. Diagnostic tests, including blood tests and skin biopsy, were performed to determine the cause of the skin lesions. However, there were no specific indications of vasculitis in the skin biopsy. The skin lesions were diagnosed as a rare extrahepatic manifestation of HBV and steroid treatment was initiated after histological examinations ruled out vasculitis. With continuous antiviral therapy and steroid administration, liver function and skin lesions improved rapidly, and she was discharged without developing ulcers.

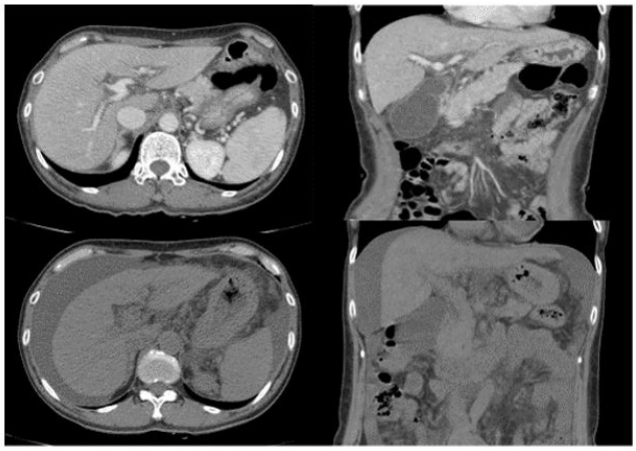


Figure1. (A) Contrast enhanced abdomen and pelvis computed tomography shows widening of porta hepatis, splenomegaly, and edematous change of GB. (B) Non-enhanced abdomen and pelvis computed tomography shows massive increased ascites.

Conclusions: The exact pathophysiology of the development of extrahepatic manifestations is not yet fully understood, but it is believed that immune complexes triggered by immune activation or a rapid increase in viral load due to reactivation of HBV may play a role. In this case, the cutaneous manifestations worsened despite antiviral treatment, histological examination excluded vasculitis, and serological tests did not reveal any other cause other than the acute phase of hepatitis B. Therefore, it is reasonable to consider this as an extrahepatic manifestation of HBV. In conclusion, although rare, extrahepatic manifestations involving the skin and mucosa can occur in CHB patients despite NUC administration, and symptom improvement can be expected through steroid treatment. Clinicians need to better understand the complex systemic nature of HBV infection and take a more holistic approach to managing patients.

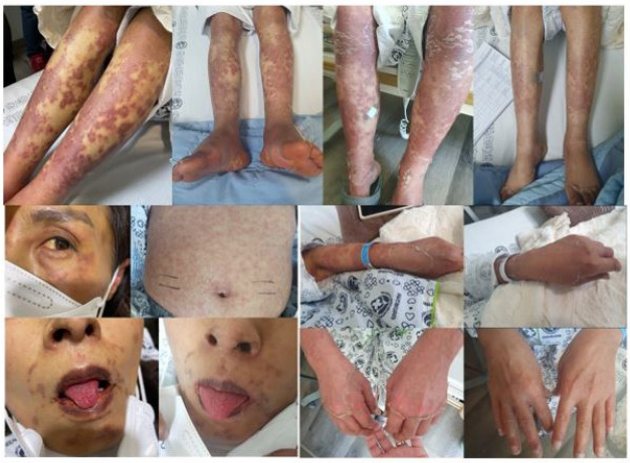


Figure2. Improvement of patient's skin and mucosal lesions following steroid therapy for control.

Keywords: HBV, Extrahepatic manifestations, Steroid, Skin

PE-39

The Change of HBCrAg in Patients with Hepatitis B before and after Treatment with Tenofovir Disoproxil Fumarate

Le Hien[1], Nguyen Khac Hung Manh[1], Le Quoc Tuan[2]

[1]Nguyen University of Medicine and Pharmacy, [2]103 Cam Khe Clinic, Vietnam

Background: Hepatitis B virus (HBV) cannot be eliminated completely from infected hepatocytes because of the presence of intrahepatic covalently closed circular DNA (cccDNA). Serum biomarkers are noninvasive and valuable for the management of Hepatitis B. Hepatitis B core-related antigen (HBcrAg) correlates with serum HBV DNA and intrahepatic cccDNA. HBcrAg is used for manegement intrahepatic viral replicative activity.

Aims: Survey on the change of HBcrAg in patients with chronic hepatitis B before and after treatment with Tenofovir disoproxil fumarate 300mg.

Methods: A cross-sectional descriptive study was carried out on patients with hepatitis B at the 103 Cam Khe Clinic during the period from May 2020 to April 2023.

Results: Serum HBcrAg concentration gradually decreased over time of treatment, from 5.92±1.25 initially to 5.49±1.51 after 3 months, 5.02±1.38 after 6 months and 4.91±1.29 after 12 months, the difference was statistically significant in serum HBcrAg levels at 3, 6 and 12 months compared with baseline (p<0.001). In both HBeAg-positive and HBeAg-negative groups, serum HBcrAg levels also decreased

gradually with the time of treatment.

Conclusions: The HBcrAg biomarker should be introduced into routine clinical practice for the management, monitoring and prognosis of the patients with chronic hepatitis B.

Keywords: HBcrAg, Hepatitis B, Tenofovir disoproxil fumarate

PE-40

State of Fibrosis Following NA Therapy in Patient with Chronic Hepatitis B Virus Infection

Tegshjargal Amarjargal[1], Nandintsetseg Natsagdorj[1], Urangoo Bayasgalanbaatar[1], Chinzorig Dovdon[1], Tsend-Ayush Erdenetsetseg[1], Erdenebayar Gonchig[2], Baasanjav Davaadorj[1], Baatarkhuu Oidov[2], Amarsanaa Jazag[1]

MNUMS (Mongolian National University of Medical Sciences), Mongolia

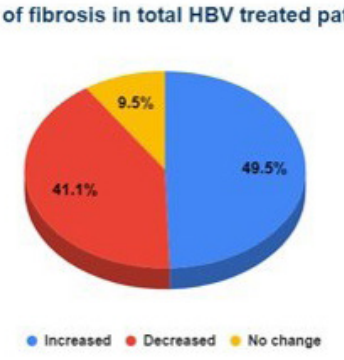
Aims: The high prevalence of hepatitis B virus disease among the population of Mongolia has become a public health problem. Chronic hepatitis B causes cirrhosis, which can progress to HCC. Alcohol abuse, obesity, and hepatitis B and C are the main causes of cirrhosis To compare cirrhosis presentations before and after drug therapy with the Fibrotouch device in clients with B virus infection.

Methods: A comparative study of progression of liver fibrosis before and during the NA therapy in patient with chronic HBV infection. Out of 1100 patients undergone NA treatment, 207 people were eligible for the study because of lack of elastography data. But out of those 96 patients fulfilled our inclusion criteria. 72 patients had taken TAF and 24 patients had taken Entecavir.

Results: 49.4% of patient who took TAF had an increase in stiffness, 40.7% decreased, and 9.9% had no change. 50% of patient who took Entecavir had an increase in stiffness after treatment, 42.9% decreased, and 7.1% showed no change. The mean duration of the drug intake was 12 months.

Conclusions: Fibrosis regression was common in many other HBV treatment studies. But in our study fibrosis progression was observed in higher rates than those of regressed. We think it might be due to short observation period, or because NAs do not clear HBsAg, or because some patients were taking alcohol during the treatment, or inflammation did not stop during the treatment

Keywords: HCC, HBV, TAF, NA



PE-41

Effects of Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide on Risk of Osteoporotic Fracture in Patients with Chronic Hepatitis B : A Nationwide Claims Study

Eunju Kim[1], Hyun Woong Lee[2], Soon Sun Kim[3], Eileen Yoon[4], Eun Sun Jang[5], Jong-In Chang[1], Young Youn Cho[6], Gi Hyeon Seo[7], Hyung Joon Kim[6]

[1]Department of Gastroenterology, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea, [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, [3]Department of Gastroenterology, Ajou University School of Medicine, Suwon, Korea, [4]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea, [5]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea, [6]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea, [7]Health Insurance Review and Assessment Service, Seoul, South Korea

Aims: Since tenofovir disoproxil fumarate (TDF) require long-term use, reduction in bone density should be considered when treating chronic hepatitis B (CHB) patients with aging and systemic diseases. Several studies have shown that patients treated with tenofovir alafenamide (TAF) had less or improved bone mineral density loss compared to patients treated with TDF. However, although improvement in bone density by taking TAF has been reported in previous studies, studies on the actual reduction of fractures are insufficient.

Methods: A retrospective cohort study was conducted on 32,582 CHB patients who were initially treated with TDF or TAF from November 2017 to December 2020 using the national claims data of the Health Insurance Review and Assessment Service. The number of patients treated with TAF and TDF was 11,705 and 20,877, respectively. The annual rate of fracture per 100 patients in each group was calculated, and the cox proportional hazard ratio (HR) was analyzed after applying inverse probability treatment weights (IPTW) for both groups

Results: Among a total of 32,582 patients, the average age was 47.8±11.2 years, males were 64.5%, and the follow-up period was 24.4±11.6 months. The incidence of osteoporotic fractures was 0.78 and 0.49 per 100 person-years in the TDF and TAF groups, respectively. After application of IPTW, HR was 0.68 (95% confidence interval 0.55–0.85, p-value=0.001).

Conclusions: In CHB patients, the risk for osteoporotic fracture was significantly lower in the TAF treatment group than the TDF treatment group.

Keywords: Chronic hepatitis B, Osteoporotic fracture, Tenofovir alafenamide

PE-42

Comparable Risk of Cardiovascular Events in Chronic Hepatitis B Patients Treated with Tenofovir Disoproxil Fumarate or Tenofovir Alafenamide

Hyeyeon Hong, Won-Mook Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Jonggi Choi

Department of Gastroenterology, Liver Center, Asan Medical Center, Universi-

ty of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Tenofovir disoproxil fumarate (TDF) is known to have lipid-lowering effect, in contrast to tenofovir alafenamide (TAF), which has a lipid-neutral effect. Therefore, concerns have been raised whether these different lipid changes affect long-term cardiovascular risk. We aimed to evaluate the long-term risk of cardiovascular events in chronic hepatitis B (CHB) patients treated with TAF or TDF.

Methods: We retrospectively analyzed 4,124 treatment-naïve CHB patients treated with TDF (n=3,186) or TAF (n=938) between 2012 and 2022. The primary outcome was a composite endpoint of major cardiovascular adverse events (MACE), including myocardial infarction, ischemic stroke, and hospitalization for unstable angina or heart failure. Serial changes in lipid profiles between the two treatments were also explored.

Results: The median age was 50.6 years, and 60.6% of the patients were male. At baseline, 382 (9.3%) and 590 (14.3%) of the patients had diabetes and hypertension, respectively. A total of 41 MACE occurred, with an annual incidence of 0.2%/100 person-years (PYs). At 1, 3, and 5 years, the cumulative risk of MACE was 0.4%, 0.8%, and 1.2% in patients treated with TDF, and 0.2%, 0.7%, and 0.7% in patients treated with TAF, respectively. No statistically significant difference in the risk of MACE between the TAF and TDF treatments (p=0.596). Older age, diabetes, history of coronary artery disease, and current smoking were associated with an increased risk of MACE in multivariable analysis.

Conclusions: Patients treated with TAF had a comparable risk of MACE as patients treated with TDF.

Keywords: Tenofovir alafenamide, Tenofovir disoproxil fumarate, Lipid profile, Cardiovascular risk

PE-43

Comparable Risk of Renal Dysfunction between Entecavir and Tenofovir Alafenamide in Patients with Chronic Hepatitis B

Yeojin Lee[1], Jiwon Yang[2], Hyeyeon Hong[2], Sung Won Chung[2], Minjoo Cho[1], Won-Mook Choi[2], Danbi Lee[2], Ju Hyun Shim[2], Kang Mo Kim[2], Young-Suk Lim[2], Han Chu Lee[2], Jonggi Choi[2]

[1]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [2]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: A previous study suggested a higher risk of renal function decline with entecavir (ETV) compared to tenofovir alafenamide (TAF) in treatment-naïve patients with chronic hepatitis B (CHB). However, the sample size was limited. This study aimed to compare the risk of renal dysfunction between ETV and TDF in a large-scale hospital cohort of treatment-naïve CHB patients.

Methods: A total of 3,343 treatment-naïve patients with CHB who received with ETV or TAF at Asan Medical Center, Seoul, Republic of Korea were included. The primary outcome was chronic kidney disease (CKD) progression, defined as an increase in CKD stage by at least one stage. CKD stage was based on the estimated glomerular filtration rate (GFR), determined using the CKD-EPI equation. Patients below 18 years old, with a history of hepatocellular carcinoma or other malignancies, baseline eGFR <60 ml/min, or follow-up duration <3 months were excluded. Multivariable Cox models were used to evaluate factors associated with CKD progression. Propensity score (PS) matching was conducted to minimize baseline characteristic differences and compare the primary outcome.

Results: Of the 3,343 patients, 2,635 (78.8%) received ETV and 708 (21.2%) received TAF. The mean age was 49.0 years in the ETV group and 49.3 years in the TAF group. Cirrhosis was present in 52.4% of the ETV group and 38.1% of the TAF group. Baseline median eGFR was significantly lower in the ETV (81.0 mL/min) than TAF group (90.0 mL/min). The prevalence of hypertension and diabetes was higher in the ETV group (5.9% and 7.9%) than TAF group (4.0% and 4.4%). Over 18,806 person-years (PYs) of observation, 207 patients experienced CKD progression, resulting in an annual incidence of 1.10 / 100 PYs. Multivariable analysis identified hypertension, diabetes, and increasing age as significant factors for CKD progression. However, treatment with TAF compared to ETV was not independently associated with the risk of CKD progression (adjusted hazard ratio: 0.87, 95% confidence interval: 0.46–1.66, p=0.68). PS matching generated 586 matched pairs and baseline characteristics were comparable between the two groups. CKD progression occurred in 36 patients treated with ETV (3,358 PYs of observation) and in 10 patients treated with TAF (1,008 PYs of observation). The annual incidence of CKD progression was 1.10 / 100 PYs in the ETV group and 0.99 / 100 PYs in the TAF group, without a statistically significant difference (p=0.08).

Conclusions: In contrast to previous report, the risk of renal dysfunction did not significantly differ between ETV and TAF in this larger historical cohort with sufficient long-term follow-up period.

Keywords: Entecavir, Tenofovir alafenamide, Renal dysfunction

PE-44

A 7th-Year Interim Anlaysis of Prospective and Longitudinal Korean Chronic Hepatitis B Cohort

Jae Seung Lee[1], Beom Kyung Kim[1], Hye Won Lee[1], Seung Up Kim[1], Do Young Kim[1], Sang Hoon Ahn[1], Sang Gyune Kim[2], Eun Young Cho[3], Young Mi Hong[4], Ki Tae Yoon[4], Yeon Seok Seo[5], Jun Yong Park[1]

[1]Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea, [3]Wonkwang University College of Medicine, Iksan, Republic of Korea, [4]Pusan National University Hospital, Busan, Republic of Korea, [5]Korea University Anam Hospital, Korea University Medical College, Seoul, Republic of Korea

Aims: We aimed to report the clinical outcome of Korean chronic hepatitis B (CHB) patients from a prospective longitudinal cohort.

Methods: This cohort, supported by the Korea Disease Control and Prevention Agency (2022E190400), was established in 2015. Voluntarily enrolled patients with CHB serially provide their clinical data and blood samples during the ten-year follow-up.

Results: From 2015 to 2022, 2949 patients (1812 male) with a mean age of 52.6 years participated in this study. Annual 16 mL of blood sampling was collected (median three times) from 1391 volunteers. Male patients had more smoking and hazardous alcohol intake (p<0.001). At the enrollment, most patients were receiving antiviral

therapy (AVT) (n=2359, 80.0%), whereas 515 (17.4%) patients were AVT-naïve. Cirrhosis was noted in 646 (21.9%) patients. The most favored AVT regimen was tenofovir disoproxyl fumarate (TDF) (40.0%), followed by entecavir (33.0%). However, during the recent two years, an increasing proportion of patients are starting the first AVT with tenofovir alafenamide (5.9% to 13.5%) or besifovir dipivoxil maleate (2.8% to 7.5%). Most patients receiving AVT with a high-genetic barrier experienced a complete virologic response (more than 80% at week 48). Crudely, the incidence of an increase in chronic kidney disease stage ≥1 was significantly higher in TDF users than ETV users (7.56 vs. 4.56 per 100 person-years, p<0.001). Hepatocellular carcinoma occurred in 33 (1.9%) patients after 50.3 months of median follow-up, most of which were within Milan criteria. Cirrhosis was independently associated with hepatocellular carcinoma occur (adjusted hazard ratio, 5.005, p=0.002).

Conclusions: This cohort study will evaluate long-term liver-related outcomes among Korean CHB patients. Future research using the cohort data and blood samples after the data purification could reveal the unmet needs to manage CHB.

Keywords: Hepatitis B, Prospective cohort, Antiviral therapy, Korea disease control and prevention agency

PE-45

How Effective Is the Method of Treating Hepatitis B with Temulawak?

Andi Nursanti

Andini Persada College of Health Sciences, Indonesia

Aims: Hepatitis B is an inflammatory disease of the liver that occurs due to infection with the hepatitis B virus. The disease causes symptoms such as fever, headache, nausea, vomiting, weakness, and jaundice. One of the diseases that temulawak is said to cure is hepatitis B. The aim of this study is to describe how effective it is to treat hepatitis B with temulawak.

Methods: The researched method is the narrative method by grouping the data from journal articles, the extraction results are similar according to the results measured to answer the objectives. Materials include research journals published related to hepatitis B and temulawak.

Results: Temulawak (Curcuma xanthorrhiza) is a widely found in Indonesia. Extracts from temulawak rhizomes contain the active ingredient curcumin. This curcumin component is what gives temulawak its yellow color. In treating hepatitis, curcumin acts as a liver protector (hepatoprotection). The hepatoprotective mechanism in temulawak occurs due to its antioxidant effect. As an antioxidant, curcumin can fight free radicals obtained from by-products of inflammation in the liver. Thus, this antioxidant can prevent liver cell damage from getting worse. In addition, in patients with hepatitis B, curcumin can also inhibit gene expression and replication of the hepatitis B virus. The reason is, in people with hepatitis B, the virus that infects them will carry out gene expression and proliferation. Animal tests modeled a group of mice suffering from hepatitis. showed hepatic cell damage and inflammation in the hepatic tissue. In the group of mice given temulawak rhizome extract, it was seen that the number of hepatocyte cells that experienced damage/degeneration decreased compared to mice without the administration of temulawak rhizome extract. Giving temulawak rhizome extract also reduced the number of lymphocyte inflammatory cells in the liver tissue of mice that received temulawak rhizome extract.

Conclusions: Thus, people with hepatitis B can avoid more severe liver disease through this temulawak medicine by consuming 2-3 times a day.

Keywords: Effectiveness, Hepatitis B, Temulawak

[Hepatitis B: Diagnostics and Biomarkers]

PE-46

The Correlation between Interleukin-6 and the Progression of Chronic Hepatitis B

Mohamed Shafi Bin Mahboob Ali

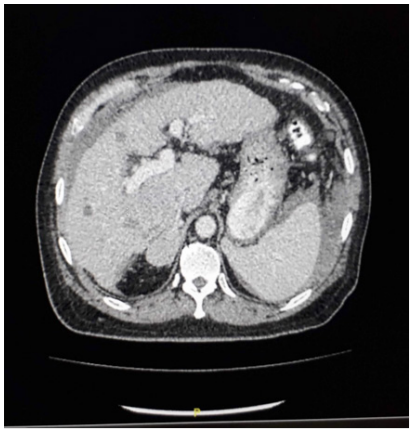
Advanced Medical and Dental Institute (AMDI), Malaysia

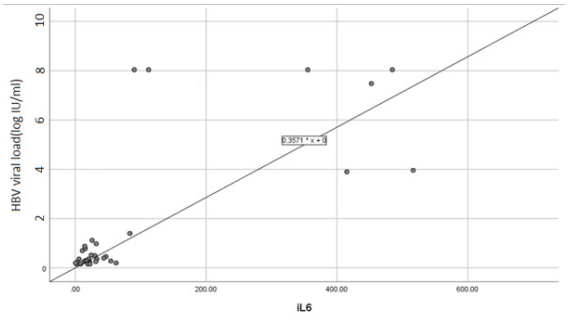
Aims: Hepatitis B virus (HBV) is a dreadful virus with the potential to cause human liver diseases such as self-limiting acute hepatitis, chronic hepatitis, fulminant hepatic failure, liver cirrhosis and hepatocellular carcinoma (HCC). These complications resulted from an immune response of the host that affects both outcome and disease progression, rather than a direct cytopathic effect. Cytokines have been shown to be engaged in regulating hepatocyte functions, and play an important role in HBV infection immunopathogenesis. Among these cytokines, Interleukin 6 (IL-6) which is a glycosylated protein, plays a major role in the progression and chronicity of HBV. Our aim of this study is to determine the correlation between IL-6 and the progression of the HBV disease in our centre.

Methods: About 52 subjects ranging from 18 years old to 80 years old that were diagnosed with HBV were recruited into the studies. Their venous blood was taken and centrifuged at 4500rpm for 5 minutes to separate the blood components. The patient's sera were withdrawn and divided into two aliquots and kept in a special fridge with a temperature of -20 to -70 degrees. The first group of sera were subjected to a hybrid capture, tube-based signal amplification using HBV Digene Hybrid-Capture I, Digene Corporation, USA. While the second group of sera were subjected to a sandwich-ELISA test using LEGEND MAX Deluxe set human IL-6 kit to quantify the IL-6 levels. Both

data were recorded and analysed using IBM SPSS version 26 software.

Results: We found that there was a direct correlation between the severity of HBV viral load and the level of IL-6. The more severe the infection, the higher the IL-6 level(p<0.05) taking the mean value of IL-6 as 132.6pg/ml. Demographical data distributions showed that men, aged between 40-60years old and healthcare workers were the risk factors to develop chronic HBV. A linear scatter plot was derived between the levels of IL-6 and HBV viral load. Pearson correlation coefficient showed a linear correlation between the two variables. The patient's ALT enzyme was used to stratify the severity of the liver functions. Higher levels of IL-6 were detected in the subjects with HBV for longer than 6 months which proved that IL-6 levels correspond to the chronicity of the disease.





Conclusions: IL-6 is a vital mediator of inflammation and the acute phase response of the liver. Our studies proved that serum IL-6 levels were positively correlated with HBV disease severity and chronicity. Thus, IL-6 may be a useful indicator of disease activity and therapeutic efficacy in patients suffering from hepatitis B. Having this key information, we may use IL-6 as the target of therapeutic interventions aimed at reducing the progression of HBV disease. Drugs that can block the activities of IL-6 may be developed to combat the destruction of the liver cells by HBV and thus, cessation of the illness. This study may become the pioneer study in the development of anti-IL-6 drugs in the future and thus, the cure of HBV liver diseases.

Keywords: Correlation, Interleukin-6, Chronic, Hepatitis B

PE-47

Performance of the Elecsys HBeAg Quant Assay against a Seroconversion Panel

Kristin Meyer-Schlinkmann[1], Elena Unruh[1], Tanja Schneider[2], Christian Voitenleitner[3]

[1]Labor Krone, Bad Salzuflen, Germany, [2]Roche Diagnostics GmbH, Penzberg, Germany, [3]Roche Diagnostics International Ltd, Rotkreuz, Switzerland

Aims: Hepatitis B e antigen (HBeAg) can be used to assess seroconversion, an important clinical endpoint with prognostic utility. Whereas qualitative HBeAg is a marker of chronic hepatitis B infection, quantitative methods can predict treatment outcomes and help identify the correct chronic hepatitis disease stage. Here, we evaluated the seroconversion sensitivity of the Elecsys® HBeAg quant assay, which, to our knowledge, has not been reported to date.

Methods: The performance of the Elecsys HBeAg quant assay was evaluated at Labor Krone, Bad Salzuflen, Germany, between January 2021–July 2021 using 3908 clinical samples (including n=245 for quantitative method comparison) and a 9-fold serial dilution of WHO standard. The Elecsys HBeAg quant assay was compared against the Elecsys HBeAg (qual) assay, the Abbott Alinity® HBeAg qual assay, and the Diasorin LIAISON® HBeAg assay. Seroconversion sensitivity was assessed using eight seroconversion panels comprising 141 members. All samples were tested once on each platform.

Results: In all seroconversion panels, the Elecsys HBeAg quant assay showed equal sensitivity compared with the Elecsys HBeAg (qual) assay, regarding the ability to detect the earliest and latest) reactive bleed draw. Compared with Alinity HBeAg, Elecsys HBeAg quant showed greater seroconversion sensitivity in 6/8 tested panels. The LIAISON HBeAg assay detected HBeAg earlier in 5/8 seroconversion panels and later in three cases than the Elecsys HBeAg quant assay. Of all assays, Elecsys HBeAg quant had the broadest measuring range and allowed quantitative analysis between 0.23–3600 IU/mL, compared with Alinity HBeAg 0.59–700 IU/mL and Liaison HBeAg 0.1–120 IU/mL.

Conclusions: The Elecsys HBeAg quant assay demonstrated equal seroconversion sensitivity compared with the Elecsys HBeAg (qual) assay, and the broadest measuring range among all comparator assays assessed.

Keywords: Hepatitis B e antigen, HBeAg, Seroconversion sensitivity, Quantitative, Elecsys, Prognostic utility, Measuring range

PE-48

Comorbidities in Indian Hemodialysis Patients with Chronic Hepatitis B and Hepatitis C

Ravi Kumar[1#], Pramod Kumar Sharma[2], Raj Kumar Sharma[3]

Corresponding and presenting author

[1]Onco Biomedical and Research Services, Gurugram, Haryana, India, [2]School of Medical and Allied Health Science, Galgotia University, Greater Noida, Up, India, [3]Collge of Paramedical Sciences, IIMT University, Meerut, UP, India

Aims: Hemodialysis patients are more likely to contract the hepatitis B virus (HBV) and the hepatitis C virus (HCV). Infections with HBV and HCV increase the likelihood of developing advanced liver

disease and extrahepatic symptoms. Investigating hepatic and extrahepatic comorbidities in hemodialysis patients with HBV and HCV infections in comparison to those without viral hepatitis was the goal of this study.

Methods: A total of 3820 hemodialysis patients from 46 hemodialysis centres were enrolled, including 318 HCV viremic patients (HCV group), 434 seropositive for HBV surface antigen (HBsAg, HBV group), and 3068 seronegative for both anti-HCV and HBsAg (non-B and non-C [NBNC] group). According to the International Classification of Diseases, comorbidities can be divided into 8 groups.

Results: The average age of the 3820 patients was 64.6 years, and 52.7% of them were male. 96% of patients had at least one comorbidity, and each patient had an average of 2.9±1.5 comorbidities. Diabetes, ischemic heart disease, and hypertension were the three most prevalent comorbidities. The HCV group had a mean of 3.3±1.7 comorbidities per person, which was considerably greater than the HBV group's (2.7±1.5, P 0.001) and NBNC group's (2.9±1.5, p=0.004). This was mostly because ischemic heart disease, respiratory problems, and mental/behavioral disorders were more common in the HCV group. Comorbidity loads were comparable across the NBNC and HBV groups.

Conclusions: Multiple comorbidities were very common in hemodialysis patients. HCV hemodialysis patients showed a higher burden of comorbidities than HBV and NBNC patients, particularly ischemic heart illnesses, diabetes, respiratory disorders, and mental/behavioral disorders.

Keywords: Comorbidities, Hemodialysis, Hepatitis B virus, Hepatitis C virus

PE-49

Diagnostic Efficacy of Serum Asialo α1-Acid Glycoprotein Levels for Advanced Liver Fibrosis and Cirrhosis in CHB: A Prospective Cohort Study

Eunho Choi, Yoon Seok Lee, Young-Sun Lee, Ji Hoon Kim, Sun Young Yim, Young Kul Jung, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun

Department of Internal Medicine, Korea University College of Medicine

Aims: Serum Asialo α1-Acid Glycoprotein (AsAGP) is a novel biomarker specific for liver fibrosis. However, the diagnostic performance of AsAGP has not been fully validated in patients with chronic hepatitis B (CHB). The aim of this study to evaluate the diagnostic efficacy of serum AsAGP level in differentiating fibrosis stage and cirrhosis.

Methods: A total of 138 subjects with CHB were prospectively enrolled. Of the 135 subjects, we analyzed 75 who underwent magnetic resonance (MR) elastography. Fibrosis stage was classified based on liver stiffness values measured by MR Elastography. (F0 <2.56kPa, F1 ≥ 2.56kPa, F2 ≥ 2.57kPa, F3 ≥ 2.92kPa, F4 ≥ 3.67kPa). We compared serum AsAGP level according to fibrosis stage and evaluated diagnostic performance of differentiating advanced fibrosis and cirrhosis.

Results: Serum AsAGP level was significantly different between fibrosis stage (F0: 1.23±0.44 μg/ml, F1: 0.96±0.07 μg/ml, F2: 0.99±0.18 μg/ml, F3: 1.20±0.28 μg/ml, F4: 1.28±0.41 μg/ml; p=0.021). We performed area under the receiver operating characteristics (AUROC) for evaluating diagnostic efficacy of AsAGP according to F1-2 vs F3-4 and F1-3 vs F4. AUROC of F1-2 versus F3-4 was 0.606 (p=0.14). The optimal cut-off level was 1.307 μg/ml (sensitivity 37.3 %, specificity 87.5 %) AUROC of F1-3 versus F4 was 0.585 (p=0.20). The optimal cut-off level was 1.409 μg/ml (sensitivity 38.5%, specificity 88.9%)

Conclusions: The serum levels of AsAGP were not found to be significant in differentiating fibrosis stages as classified by MR elastography. Larger cohort study and further research on optimal CHB stiffness cutoff levels for MR elastography are needed.

Keywords: Chronic hepatitis B, MR elastography, AsAGP

PE-50

Development of the Artificial HBV cccDNA System for Drug Screening

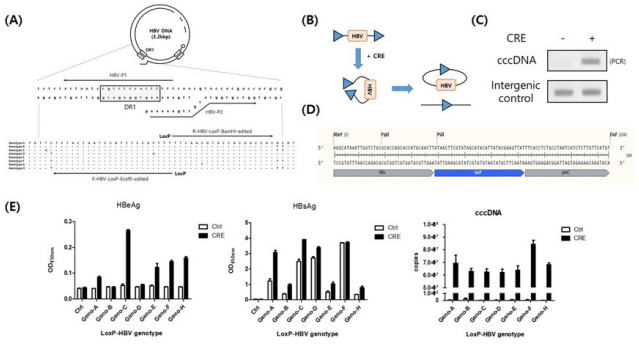
Yongwook Choi, Gahee Kim, Yong Kwang Park, Wonhee Hur, Songmee Bae

Division of Chronic Viral Diseases, Center for Emerging Virus Research, National Institute of Infectious Diseases, Korea National Institute of Health, Chungbuk, Korea

Aims: Despite of efficient nucleotide analog drugs, covalently closed circular DNA(cccDNA) is the important barriers for HBV cure and is hard to study because of low copy numbers even in the primary human hepatocyte(PHH). In this study, we established and tested the screening system using the artificial HBV cccDNA in cell line and mouse model.

Methods: HBV constructs (3.2kbps) with loxP sequence (34bps) in each ends were amplified from HBV-infected sera (Genotype A,B,C,D,E,F,H) and inserted into the pUC19 by in-fusion cloning. Flag-tagged CRE gene cloned into the pFLAG-CMV2 vector was used for establishing the artificial cccDNA by recombination of loxP site. Established artificial cccDNA was detected by qRT-PCR using designed for amplifying the recombinated cccDNA. Concentrated HBV virus particle from upper system was tested for re-infection test in HepG2-NTCP cell line. IFN-α(2a), lymphotoxin-$\alpha_1\beta_2$, and adefovir were treated for testing this system. Also, it was tested in the loxP-HBV hydrodynamic injected Alb-cre mouse model by ELISA for HBeAg and HBsAg.

Results: Designed primers using conserved sequence in HBV genotypes were amplified by seven HBV genotypes, then each loxP-HBV constructs were established. Each construct was tested in the flag-cre co-transfected HepG2 cells by ELISA for HBeAg and HBsAg, by quantification of cccDNA. Here, HBV genotype C was higher HBeAg then others, but HBV cccDNA was nearly same to Genotype A to H, except F. Finally selected HBV genotype C was further tested with ELISA assay for HBeAg and qRT-PCR for cccDNA using previously reported HBV drugs, such as IFN-α(2a), lymphotoxin-$\alpha_1\beta_2$, and adefovir(ADV). Then, we found that the artificial cccDNA could produce the infectious HBV particle. Finally, this system was confirmed in the mouse model using DNA or adenoviral loxP-HBV hydrodynamic injection.



Development of the screening system for targeting the HBV cccDNA (A) Diagram of primers for loxP-HBV(Genotype A to H) (B) LoxP-CRE system for artificial HBV cccDNA (C,D) Analysis of PCR and sequencing of artificial HBV cccDNA (E) Analysis of the artificial HBV cccDNA from Genotype A to H with ELISA for Hbe-, HBsAg and quantification of cccDNA

Conclusions: In this study, we established and tested the easy system for the artificial HBV cccDNA *in vitro* and *in vivo* model, overcoming the barrier for cccDNA study. Also, we showed that this system is acceptable for seven HBV genomes, representing the possibility for the screening of patient specific drugs. We will further study the cccDNA-specific drug screening from chemical libraries by this system and improve it as a screening cell line having the inducible cre expression with loxP-HBV. This work was supported by the intramural fund (grant numbers 2022-NG-004-01) from Korea National Institutes of Health.

Keywords: Hepatitis B virus, HBV, CccDNA

[Hepatitis B: New Therapies and Trials]

PE-51

Clinical and Virusological Outcomes of Tenofovir Alafenamide Treatment in Patients with Hepatitis B Virus Infection

Tuvshinbayar N[1,2], Amaraa R[1], Burmaajav B[2], Gegeebadrakh[1], Baatarkhuu O[3]

[1]Department of Gastroenterology, State Second Central Hospital, Ulaanbaatar, Mongolia, [2]Ach"Medical University, Ulaanbaatar, Mongolia, [3]Department of Infectious Diseases, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

Introduction: WHO estimates that 296 million people were living with chronic hepatitis B infection in 2019, with 1.5 million new infections each year. The latest data shows that 10.6-11.6 % of Mongolian population are infected with hepatitis B virus infection.

Goal

Evaluate the clinical and virological outcome of tenofovir alafenamide treatment in patients with hepatitis B infection.

Methods: The clinical trials have evaluated TAF in HBeAg positive and HBeAg negative HBV patients. The trials have similar design and randomized,Single-blind, the subjects are unaware of which group they have been assigned to studies. The primary efficacy endpoint was the proportion of patients with HBV-DNA<29IU/ml at weeks 96. Other virological result endpoints were the proportion of patients with HBsAg seroconversion at weeks 96.

Results: The virologic endpoints, an HBV-DNA <29 IU/ml at weeks 96, was achieved by 243(79.1%) receiving TAF, 111(75.4)% of patients which were non-inferior to the 106(78.5%) patients receiving TDF (95% confidence interval (CI 9.7–2.5); p=0.26. After of treatment at week 96, significant higher rates of ALT normalization was seen in the TAF group compared to the TDF group (209(68%) "vs" 83(56.4%) "vs" 82(60.8%), p=0.001) Result: At 96 weeks of treatment, patients receiving TAF hed significantly smaller reductions in bone mineral density(BMD) compared with patients receiving TDF. At weeks 96, median changes in eGFR were signifi-cantly smaller in the TAF recipients compared with the TDF recipients.

Conclusions: Data from Mongolian adult the study population show that TAF is non-inferior to TDF in efficacy in both HBeAg-negative and HBeAg-positive patients, with high rates of viral suppression overall. TAF and switching from TDF to TAF are similar efficacy and safety in long-term treatment of TDF.

Keywords: HBV-DNA, Tenofovir alafenamid fumarate, qHBsAg, HBeAg

PE-52

Evaluation of Sequential Therapy Peg-Interferon and Nucleos(t)ide Analogue Compared to Monotherapy in Patients with Chronic Hepatitis B

Roland Helmizar, Nana Liana[1], Ruhsyahadati Ajisman[2], Rahma Triyana[3]

Department of Internal Medicine, Faculty of Medicine Baiturrahmah University, Padang, Indonesia, [1]Department of Anatomic Pathology, Faculty of Medicine Baiturrahmah University, Padang, Indonesia, [2]Department of Clinical Microbiology, Faculty of Medicine Baiturrahmah University, Padang, Indonesia, [3]Department of Parasitology, Faculty of Medicine Baiturrahmah University, Padang, Indonesia

Aims: Chronic Hepatitis B (CHB) remains a significant global health issue that can result in the development of liver cirrhosis and hepatocellular carcinoma (HCC). It is crucial to monitor patients with chronic hepatitis B infection to identify any changes in the disease's progression, such as HBsAg seroconversion. While Nucleos(t)ide Analogue (NA) is known for effectively suppressing viral load, its long-term use poses a high risk of resistance. Therefore, an alternative treatment approach could involve adding an immunomodulator. This study aimed to evaluate the response at the end of sequential therapy (NA and Peg-IFN) compare with monotherapy in suppressing HBsAg.

Methods: A systematic search through Pubmed/MEDLINE, Scopus, Cochrane Library, and EBSCO was conducted to find this topic. The studies were selected and critically appraised. Data were then analyzed and summarized descriptively.

Results: In a study by Zhang et al. (2019), it was found that the early combination therapy resulted in a significantly higher proportion of patients with a reduction of HBsAg levels by more than 1500 IU/mL (61/108, 56.5%) compared to the NA monotherapy group (63/151, 41.7%). This suggests that the combination therapy may be more effective in reducing HBsAg levels. Similarly, Heng Chi (2017) observed a greater decrease in HBsAg levels in patients receiving peginterferon add-on therapy compared to those on NA monotherapy from week 0 to week 48. (−0.40 vs. −0.15 log IU/mL; p=.005). These findings indi-

cate that the addition of peginterferon to the treatment regimen may lead to better outcomes in terms of HBsAg reduction.

Conclusions: Sequential therapy (NA and Peg-IFN) can be effectively made HBsAg loss and seroconversion. But it is important to note that these findings are based on observational studies, and further research, including randomized controlled trials, would provide more robust evidence on the efficacy and safety of sequential therapy in CHB patients.

Keywords: Peg-interferon, Nucleos(t)ide analogue, Sequential therapy, Chronic hepatitis B

PE-53

Non-Viral Gene Delivery Systems: Harnessing Nanotechnology for Therapeutic Applications in Hepatitis-B Infection

Avinash kumar[1], Ashok Kumar Sah[2]

[1]Department of Paramedical and Allied Health Sciences, Galgotias University, India

Aims: In order to treat hepatitis-B (HBV) infection, this study sought to examine the possibilities of non-viral gene delivery methods utilising nanotechnology. The goal was to create a novel strategy for treating HBV infection by examining the effectiveness and safety of various nanocarriers in delivering therapeutic nucleic acids to hepatocytes.

Methods: A thorough literature analysis was carried out to understand the most recent advancements in non-viral gene delivery technologies for HBV therapy. In order to find different nanocarriers for delivering therapeutic nucleic acids, such as plasmids containing antiviral drugs or RNA interference (RNAi) constructs targeting viral gene expression, important research publications, reviews, and clinical trials from reliable sources were evaluated. Various delivery methods' efficacy was examined in HBV-infected animal models and human clinical trials. The safety profiles, including possible immune responses and off-target consequences, were also thoroughly examined.

Results: The research turned up a number of non-viral gene delivery technologies with promising results for treating HBV. Among the most thoroughly investigated nanocarriers for gene delivery in HBV infection were lipid-based nanoparticles, polymer-based carriers, and dendrimers. These systems demonstrated improved cellular uptake and intracellular trafficking, which resulted in effective hepatocyte gene expression. Therapeutic nucleic acid delivery showed strong antiviral effects and inhibited HBV replication *in vitro* and *in vivo*. Examples of these nucleic acids include small interfering RNAs (siRNAs) targeting vital viral genes or plasmids expressing antiviral cytokines. The outcomes also showed that the selectivity and likelihood of off-target effects were increased when therapeutic genes were delivered to hepatocytes by surface modifications or ligand conjugation.

Conclusions: The results of this study suggest that nanotechnology-based non-viral gene delivery technologies have great promise for therapeutic uses in HBV infection. These nanocarriers have produced significant antiviral effects and inhibited HBV replication by effectively delivering therapeutic nucleic acids to hepatocytes. While reducing off-target effects and increasing specificity through targeted delivery methodologies, the overall safety profiles have been favorable for clinical translation. Non-viral gene delivery methods provide a unique strategy to treat HBV infection by using nanotechnology and gene therapy developments, possibly providing a potent replacement or addition to conventional antiviral medications. More research and optimization are necessary to solve issues including enhancing transfection effectiveness, lengthening the time that genes are expressed, and assuring long-term safety. The findings of this study highlight how crucial it is to carry out further research in the area to develop non-viral gene delivery platforms for therapeutic uses in HBV infection and other liver illnesses. As this technology develops, it may have a substantial impact on the creation of personalized treatment plans for HBV patients, which would eventually result in better clinical results and a lower worldwide burden of HBV infection.

Keywords: Non-viral gene delivery, Nanotechnology, Therapeutic, Gene therapy

PE-54

Study of Phytocompounds Targeting the Protein of Hepatitis B Virus: An Insilico Analysis

Dhananjay Yadav

Department of Life Science, Yeungnam University, Korea

Aims: Hepatitis B viruses are the most common cause of chronic disorders which lead to cirrhosis and hepatocellular carcinoma. Several medicinal plants have been used for treating potential liver problems. In this study we used *Glycyrrhiza glabra* which is known to have medicinal properties. Hence, the present work investigated in-silico information of the phytocompounds extracted from *Glycyrrhiza glabra* that targets Hepatitis B.

Methods: Crystal structures of target proteins of Hepatitis B virus such as HBx protein (PDB ID: 3 MSH) were used for the present docking study. The ligands are the phytocompounds used in the study were Benzoic acid, Colecoxib, Coumestrol, Daidzin, and Ononin. There 3D structure of were retrieved from PubChem Compound Database. Consequently, the ligands were docked to Hepatitis B protein using "Autodock 4.2." Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. We have set the AutoDock parameter and the distance-dependent dielectric functions useful for the calculation of the van der Waals and the electrostatic terms, respectively. The final figures were generated with the help of Discovery Studio Visualizer (Accelrys San Diego, CA, USA).

Results: The study result revealed that the compounds from *Glycyrrhiza glabra* showed good docking scores for Hepatitis B and can be useful for treating the diseased condition. Further, we have calculated based on minimum inhibition constant, Ki and highest negative free energy of binding with the maximum interacting surface area in the docking studies. We reported that the binding energy was highest in Coumestrol (-6.29 kcal/mol). The free binding energies were (-6.09 kcal/mol), (-4.97 kcal/mol), (-4.84 kcal/mol) and (-4.29kcal/mol) using Colecoxib, Daidzin, Ononin and Benzoic acid respectively.

Conclusions: This study might be useful in future for designing novel drugs for the treatment of Hepatitis B virus.

Keywords: Medicinal plants, Hepatitis B, Molecular docking, Phytocompounds

[Hepatitis C: Basic and Translational Research]

PE-55

Changes of Adiponectin-Leptin Ratio in Chronic Hepatitis C Patients before and after DAA Therapy: A Prospective, Multicenter Study in Korea

Jung Hoon Yoo[1]*, Gwang Hyeon Choi[1]*, Eun Sun Jang[1], Sung Hee Choi[1], Youn Jae Lee[2], Young Seok Kim[3], In Hee Kim[4], Sung Bum Cho[5], Byung Seok Lee[6], Kyung-Ah Kim[7], Woo Jin Chung[8], Sook-Hyang Jeong[1]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Republic of Korea, [2]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea,[3]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea, [4]Department of Internal Medicine, Jeonbuk National University Hospital, Jeonju, Republic of Korea, [5]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, [6]Departments of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea, [7]Departments of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang Republic of Korea, [8]Departments of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea

Aims: Some studies suggested an increase of hepatic steatosis after achieving sustained virological response (SVR) in patients with chronic hepatitis C. Recently, adiponectin-leptin (A-L) ratio is proposed as a predictor of CVD risk. Therefore, we investigated the plasma levels of A-L ratio in the Korean chronic hepatitis C patients treated with DAA at 3 time points of pretreatment (PreTx), end-of treatment (EOT) and SVR12.

Methods: Using a prospectively collected 179 plasma samples at the 3 time points from 179 patients with chronic hepatitis C virus (HCV) infection who were treated with direct acting antivirals (DAAs) (mean age 59.9, 50.3% of female, 29.7% of cirrhosis) enrolled in 8 hospitals from Mar 2020 to Jan 2022, adiponectin and leptin levels were measured and compared. In addition, factors related to low A-L ratio<0.5, which can be considered high cardiometabolic risk, were analysed.

Results: All 179 patients achieved SVR12. The A-L ratio showed negative association with pretreatment HCV RNA (R=-0.28, p=0.017) and body mass index (BMI, R=-0.5, p<0.001). The median plasma leptin level showed a transient increase of leptin level at EOT compared to PreTx (6.0, 6.6, and 6.0 ng/mL, respectively). The median plasma adiponectin level showed a significant decrease at SVR12 than PreTx level (4.0, 4.1, and 3.5 ug/mL, respectively). The median A-L ratio showed a significant decrease at EOT and SVR12 than preTx level (0.63, 0.63, and 0.56, respectively) The proportion of high CV risk groups with an A-L ratio<0.5 significantly increased to 39.1%, 44.1%, and 47.2% at PreTx, EOT and SVR12, respectively (p=0.006). Among normal A-L group (n=109), pretreatment A-L ratio (OR 0.33, p=0.024) and BMI is independently associated with transition to low A-L ratio group at SVR12 (OR 1.23, p=0.048).

Conclusions: DAA 치료 및 SVR 달성 동안 혈장 A/L 비율은 감소하는 경향이 있었으며 이는 DAA 치료 후 잠재적인 CV 위험을 시사합니다.

Keywords: Chronic Hepatitis C, Adiponectin, Leptin, DAA

PE-56

Implementation of a Community-Based Integrated Viral Hepatitis Prevention, Testing and Treatment Model for People Who Inject Drugs in Yangon, Myanmar

Mon Mon Su Naing, Bridget Draper, Hla Htay, Margaret Hellard, Thin Mar Win, Daniel O'Keefe, Mark Stoove, Alisa Pedrana, Jess Howell

Burnet Institute, Myanmar

Aims: In Myanmar, there are insufficient hepatitis-C virus (HCV) treatment services to meet national elimination goals. The COVID-19 pandemic and recent political unrest have reduced access to HCV treatment for people who inject drugs, among whom HCV prevalence remains high. This study presents implementation of a community-based integrated care model providing viral hepatitis prevention, testing, and treatment to people who inject drugs in Yangon, Myanmar.

Methods: Based on previous work implementing decentralized, community-based HCV care, we developed a similar, simplified model of care and integrated hepatitis-B virus (HBV) vaccination. Our community-based and integrated care model offers free HCV testing and treatment, HBV screening and vaccination, and needle/syringe distribution. HCV care is provided using a 'one-stop' HCV clinical pathway, including point-of-care HCV viral load testing, non-specialist guided treatment, and telemedicine specialist consultation for those requiring expert advice. HBV vaccine is given to those screening HBV negative.

Results: The clinic commenced service provision in March 2023. In two months of operation, 93 clients (aged 20 to 59) enrolled at the clinic, including 89 (96%) men and 4 (4%) women. 86 (92%) patients were eligible for treatment and were screened for HCV. Of these, 65 (76%) were diagnosed as having chronic HCV infection, and 60 (92%) being initiated onto treatment. 31 people were administered HBV vaccination and 29 people (93.5%) completed the vaccination schedule. 128 people accessed the needle/ syringe program, with 5,772 needle/syringes distributed in total.

Conclusions: Preliminary findings demonstrate high levels of HCV case detection and treatment and high uptake of HBV vaccination. Future, comprehensive evaluation of the model of care is anticipated to provide crucial information to support ongoing HCV treatment for people who inject drugs, particularly in locations with limited tertiary HCV care services. Further work is currently underway to tailor the model to better meet the needs of female who inject drugs.

Keywords: Hepatitis C virus, People who inject drugs, HCV treatment, HBV vaccination

PE-57

Investigating Cross Transmission of Hepatitis C Virus among Rare and Limited Risk Groups in Japan

Zayar Phyo[1], Ko Ko[1], Aya Sugiyama[1], Tomoyuki Akita[1], Kazuaki Takahashi[1], Satoshi Tanaka[2], Ryotaro Sakamori[2], Junko Tanaka[1*]

[1]Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Science, Hiroshima University, Hiroshima, Japan, [2]Department of Gastroenterology, National Hospital Organization, Osaka National Hospital, Osaka, Japan

Aims: The aim of this study was to explore the potential cross-transmission of hepatitis C virus (HCV) among people who inject drugs (PWID) and men who have sex with men (MSM) who are rare and limited in Japan.

Methods: This is a collaborative research between Hiroshima University and the Gastroenterology Department of the National Hospital Organization, Osaka National Hospital, Japan to investigate HCV infected patients treated at the hospital between January 2009 and February 2023. Prospective recruitment involved patients visiting the hospital from June 2022 to February 2023 while retrospective recruitment included patients who had not visited the hospital until June 2022. All patients with either PWID, MSM, or both were included. Additionally, patients with neither PWID nor MSM were randomly selected. Serum samples collected before anti-HCV treatment were analyzed at Hiroshima University. HCV RNA was extracted, full core region (576 base-pairs) was amplified and directly sequenced by Sanger method, and genotype distribution was determined by phylogenetic analysis. Ethical approval was obtained from the Ethics Review Committee of Hiroshima University and Osaka National Hospital.

Results: Total 104 patients were divided into four groups: 26 Non-MSM PWID, 14 MSM PWID, 22 MSM Non-PWID, and 42 Non-MSM Non-PWID with mean age of 44 years old. Of successfully amplified 94 samples, genotype 2a was predominant in Non-MSM PWID, whereas genotype 1b in the other groups. Phylogenetic analysis revealed strains from MSM PWID and MSM Non-PWID were closely related while those between MSM PWID and Non-MSM PWID were not.

Conclusions: This study suggests that HCV infection is transmitting between MSM PWID and MSM Non-PWID through unsafe sexual behavior. The transmission route is differed in PWID regardless of MSM. MSM status determined the transmission route among PWID. Therefore, MSM should be considered as an important target group in the effort for HCV elimination in Japan.

Keywords: HCV, PWID, MSM, Elimination, Japan

PE-58

Trends of the Prevalence of Hepatitis C Virus Infection by Region Using National Health Insurance Service from 2010 to 2022, Republic of Korea

Hwa Young Choi, Moran Ki

Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea

Aims: This study aimed to identify the trend of prevalence of hepatitis C virus (HCV) infection from 2010 to 2022 in the Republic of Korea and estimated the high-risk regions and town.

Methods: The study was used on patients registered with HCV (ICD-10 code: B17.1 or B18.2) from the claim data of National Health Insurance Service data 13 years from 2010 to 2022. And if the date between the first and second claim dates for HCV infection was within 90 days, it was included in the study subjects. We calculated the age-sex adjusted prevalence of patients with HCV using the direct method based on the resident registration population at the end of the year 2020 and conducted a comparison by region and year. Estimated annual percentage changes (EAPC) were calculated to evaluate the trends of prevalence of HCV from 2010 to 2022.

Results: The sex-, age-, and region-adjusted prevalence per 100,000 decreasing trend from 101 in 2010 to 77 in 2022. Also it decreased by 2.13% per year for 13 years. However, the case-fatality rate increasing trend from 2.8% in 2010 to 7.8% in 2022 and increased by 6.37% per year for 13 years.
According to comparison by region, the age-sex adjusted prevalence per 100,000 in 2022 was the highest in Busan (173), Jeonnam(105) and Gyeongnam(105) and comparison by town, the age-sex adjusted prevalence per 100,000 in 2022 was the highest in Busan Seo-gu (423), Busan Jung-gu (404) and Jeonbuk Sunchang-gun (377).

Conclusions: The changes in the prevalence by region and town were confirmed from 2010 to 2022. The prevalence still differs by region and is highest in Busan, Jeonnam, Gyeongnam. Also, prevalence by town highest in Busan Seo-gu, Busan Jung-gu, Jeonbuk Sunchang-gun, Jeonnam Jindo-gun and Gyeongnam Namhae-gun. Preferentially, it is necessary to develop strategies for active surveillance and treatment policies in highly prevalent regions and town.

Keywords: Hepatitis C virus, Prevalence, High-risk regions, Estimated annual percentage changes (EAPC), National health insurance service

[Hepatitis C: Clinical Aspect: Therapy]

PE-59

Prognosis of Patients with Chronic Hepatitis C Genotype 1b Infection Treated Using Daclatasvir/Asunaprevir after Sustained Virologic Response: A Six-Year Multicenter Prospective Observational Study

Jae Hyun Yoon[1], Sung Eun Kim[2], Yohan Lee[1], Gi-Ae Kim[3], Yewan Park[3], Ji Won Park[2], Seong Hee Kang[4], Young-Sun Lee[5], Jeong Han Kim[6,7]

[1]Department of Internal Medicine, Chonnam National University Hospital School of Medicine, Gwangju, Korea, [2]Department of Internal Medicine, Hallym University College of Medicine, Anyang, Korea, [3]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea, [4]Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea, [5]Department of Internal Medicine, Korea University Medical Center, Seoul, Korea, [6]Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea, [7]Research Institute of Medical Science, Konkuk University School of Medicine, Seoul, Korea

Aims: Direct-acting antiviral (DAA) therapy can cure chronic hepatitis C (CHC) and daclatasvir (DCV)/asunaprevir (ASV) is the first interferon-free DAA therapy introduced in Korea. Patients who achieve sustained virologic response (SVR) after DAA treatment are expected to have good prognoses. However, information about patients' prognoses after achieving SVR with DCV/ASV therapy is limited. Therefore, we aimed to investigate the prognosis of these patients.

Methods: This multicenter prospective observational study included patients with CHC who achieved SVR after DCV/ASV treatment, and the final follow-up date was August 2022. The primary endpoint was hepatocellular carcinoma (HCC) occurrence, and the secondary endpoints were recurrence or reinfection. These endpoints were checked once annually.

Results: This analysis included 302 patients, with a median follow-up duration of 38 months. The median age was 58 years, and 148 patients (49.0 %) were male. Cirrhosis was observed in 103 patients (34.1%), and the median Child-Pugh score was 5.0 HCC occurred in 16 patients (5.3%) within 6 years after SVR; patients with HCC were older and had higher cirrhosis prevalence, AFP, and FIB-4 scores. Cox proportional hazards analysis revealed that age >71 years old (p=0.005) and cirrhosis (p=0.035) were significant variables. Recurrence or reinfection occurred in two patients (0.7%) within 1 year after SVR

Conclusions: Although the prognosis of patients who achieved SVR was generally good, the HCC risk was not completely eliminated, especially in older and cirrhotic patients. Additionally, recurrence or reinfection is possible. Hence, regular follow-up surveillance after achieving SVR and early treatment is warranted

Keywords: Hepatitis C, Sustained virologic response, Daclatasvir, Asunaprevir

PE-60

Potential Antiviral siRNA Molecules for Silencing the 3'UTR of Hepatitis C Virus Genotype 1

Rian Ka Praja

Department of Microbiology, Faculty of Medicine, Universitas Palangka Raya, Central Kalimantan, Indonesia

Aims: Nowadays, hepatitis C virus (HCV) infection is still a key contributor to cirrhosis of the liver, hepatocellular cancer, and liver transplantation. Therefore, an effective antiviral drug is needed to treat the HCV infection. This study aimed to design small interfering RNAs (siRNAs) for silencing the 3'-untranslated region (3'UTR) of HCV genotype 1.

Methods: siRNA molecules were designed using siDirect. A multistep filtering bioinformatics approach was implemented to select potential antiviral siRNAs against the 3'UTR of HCV genotype 1. A siRNA Scales tool was employed to screen siRNA candidates. Then, siRNA candidates were further analyzed using MaxExpect and DuplexFold to calculate the free energy of folding of the siRNAs and the free energy of binding between the guide strand and the target, respectively. The efficacy of siRNAs was predicted using SMEPred.

Results: In this study, 11 siRNAs were successfully designed based on the complete genome of HCV genotype 1 (NCBI Accession Number: NC_004102.1). Further analyses using multiple bioinformatics tools showed that only four potential siRNAs possessed efficacy to silence the 3'UTR of HCV genotype 1 with the highest efficacy level of 84.5.

Conclusions: This study successfully discovers four potential siRNA molecules which might be used as a potential antiviral siRNA-based therapy to suppress HCV genotype 1 infection. However, the predicted siRNAs in this study are essential to be validated using laboratory experiments.

Table 1. siRNAs predicted for the 3'UTR region of HCV genotype 1 and their parameters.

get ion	Target sequence 21nt target + 2nt overhang	RNA oligo sequences 21nt guide (5'→3')	RNA oligo sequences 21nt passenger (5'→3')	siRNA Scales	MaxExpect	DuplexFold	siRNA Efficacy
50	AGGCCATTTCCTGTTTTTTTTTT	AAAAAAAACAGGAAAUGGCCU	GCCAUUUCCUGUUUUUUUUUU	11	1.9	-26.4	63
51	GGCCATTTCCTGTTTTTTTTTT	AAAAAAAAACAGGAAAUGGCC	CCAUUUCCUGUUUUUUUUUU	16	1.8	-23.5	62.8
52	GCCATTTCCTGTTTTTTTTTT	AAAAAAAAAACAGGAAAUGGC	CAUUUCCUGUUUUUUUUUU	13	1.9	-22	63.6
57	TTCCTGTTTTTTTTTTTTTTTT	AAAAAAAAAAAAAACAGGAA	CCUGUUUUUUUUUUUUUUUU	15	None	None	None
58	TCCTGTTTTTTTTTTTTTTTT	AAAAAAAAAAAAAAACAGGA	CUGUUUUUUUUUUUUUUUU	15	None	None	None
60	CTGTTTTTTTTTTTTTTTTT	AAAAAAAAAAAAAAAACAG	GUUUUUUUUUUUUUUUUUU	16	None	None	None
130	TTCCTTTTTTTTTTTTTTTTT	AAAAAAAAAAAAAAAAGGAA	CCUUUUUUUUUUUUUUUUU	13	None	None	None
131	TCCTTTTTTTTTTTTTTTTTT	AAAAAAAAAAAAAAAAAGGA	CUUUUUUUUUUUUUUUUUU	15	None	None	None
152	TTCTTTCCTTCTTTTTTCCTTTC	AAGGAAAAAAGAAGGAAAGAA	CUUUCCUUCUUUUUUCCUUUC	19	None	None	None
157	TCCTTCTTTTTTCCTTTCTTTTC	AAAGAAAGGAAAAAAGAAGGA	CUUCUUUUUUCCUUUCUUUUC	13	None	None	None
172	TTCTTTTCCTTCCTTCTTTAATG	UUAAAGAAGGAAGGAAAAGAA	CUUUUCCUUCCUUCUUUAAUG	14	1.8	-27.8	84.5

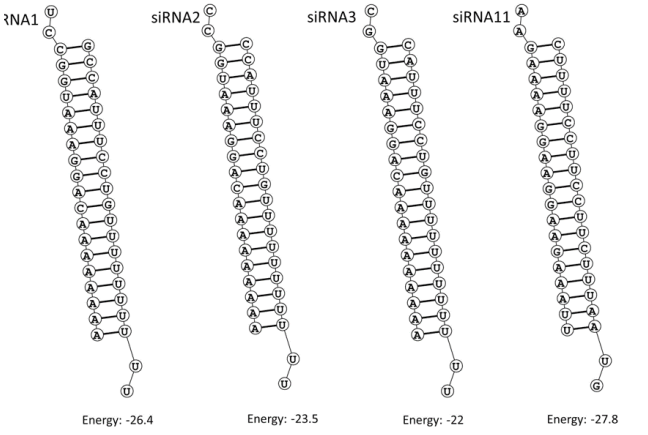


Figure 1. Lowest free energy structures of guide strands of siRNAs with their corresponding target regions and their energy values.

Keywords: 3'-Untranslated region (3'UTR), Bioinformatics, Hepatitis C virus (HCV), Small interfering RNA (siRNA)

PE-61

Evaluation of Machine Learning Algorithms for Predicting Direct-Acting Antiviral Treatment Failure among Patients with Chronic Hepatitis C Infection

Haesuk Park[1]*, Wei-Hsuan Lo-Ciganic[1], James Huang[1], Yonghui Wu[2], Debbie Wilson[1], Linda Henry[1], Joy Peter[2], Mark Sulkowski[3], David R. Nelson[2]

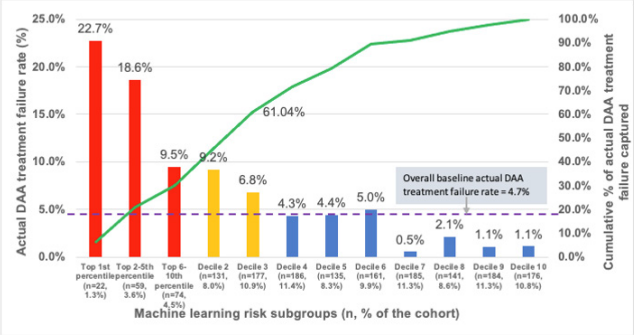
[1]Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, Florida [2]Department of Medicine, University of Florida, Gainesville, Florida [3]Johns Hopkins Medicine, Baltimore, Maryland, United States

Aims: Despite the availability of efficacious direct-acting antiviral (DAA) therapy, the number of people infected with hepatitis C virus (HCV) continues to rise, and HCV remains a leading cause of liver-related morbidity, liver transplantation, and mortality. We developed and validated machine learning (ML) algorithms to predict DAA treatment failure using predictors occurring before and during treatment.

Methods: Using the HCV-TARGET (Hepatitis C Therapeutic Registry and Research Network) registry of adults with HCV who initiated

all-oral DAA treatment, we developed ML algorithms including elastic net (EN), random forest (RF), gradient boosting machine (GBM), and feedforward neural network (FNN). Model performances were compared with multivariable logistic regression (MLR) by assessing C statistics and other prediction evaluation metrics (e.g., sensitivity, specificity, and number needed to evaluate).

Figure. Electric net model assessment of direct-acting antiviral treatment failure for each decile risk subgroup



Results: Among 6525 HCV-infected adults (training sample: n=4,894 and validation sample: n=1,631; mean age=57 years; 60% male; 23% Black and 66% White), 4.7% experienced DAA treatment failure. All 4 ML models performed similarly in predicting DAA treatment failure (C statistic [95% CI]: EN, 0.74 [0.69-0.79]; RF, 0.74 [0.69-0.80]; GBM, 0.72 [0.67-0.78]; FNN, 0.75 [0.70-0.80]), and outperformed MLR (C statistic [95% CI]: 0.51 [0.46-0.57]). EN used the fewest predictors (n=27). With the Youden index, the EN had 58.4% sensitivity and 77.8% specificity, and 9 patients were needed to identify 1 DAA treatment failure. Over 60% of treatment failures were classified in the top 3 risk decile subgroups. EN-identified predictors included male sex, treatment <8 weeks, treatment discontinuation due to adverse events, albumin level <3.5 g/dL, total bilirubin level >1.2 g/dL, advanced liver disease, and use of tobacco, alcohol, or vitamins.

Conclusions: Machine learning algorithms have the potential to inform public health policies regarding curative treatment of HCV. Addressing modifiable factors of DAA treatment failure may reduce the burden of retreatment.

Keywords: HCV, Direct-acting antivirals, Treatment failure, Machine learning

PE-62

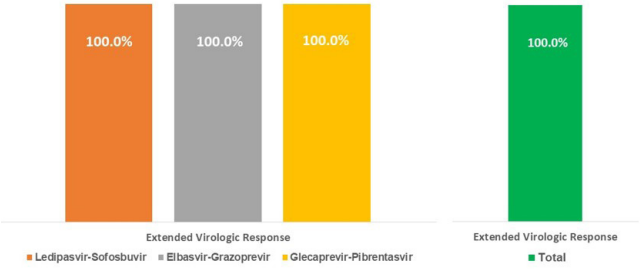
Long-Term Durability of Direct-Acting Antiviral Therapy: Extended Virological Response Maintained for 12 Months in Hepatitis C Patients

Young Hyeon Ahn, Sae Hwan Lee, Hong Soo Kim

Department of Gastroenterology, Soonchunhyang University Cheonan Hospital, Cheonan, Korea

Aims: Sustained virological response (SVR) in hepatitis C virus (HCV) treatment is defined as the absence of detectable HCV RNA in the blood for at 12 weeks after direct-acting antiviral (DAA) therapy. While SVR typically indicates successful viral eradication of HCV, rare instances of late relapse or reinfection can occur. This study aimed to investigate the durability of virological response in patients with SVR after DAA therapy.

Methods: A total of 122 patients who received DAA treatment for HCV at Soonchunghyang University Cheonan Hospital between 2017 and 2021 were consecutively enrolled in this study. Among them, 19 patients received elbasvir/grazoprevir, 37 received ledipasvir/sofosbuvir, and 66 received glecaprevir/pibrentasvir. Patients underwent baseline laboratory tests before treatment initiation and were re-evaluated at the end of treatment, as well as at 12 weeks to determine SVR, and at 12 months post-SVR, defined as extended virological response (ExtVR).



Results: The median age of the patients was 56 years (range: 17-88), and 69% were female. The baseline HCV RNA level had a median of 5.9 log IU/mL (range: 3.5-7.4). Among the patients, 60 had genotype 1b, 61 had genotype 2, and 1 had genotype 3. Five patients had prior interferon experience, and 6 patients had cirrhosis. Median follow-up period was 54 (range: 44-74) weeks after SVR. All patients achieved end-of-treatment response, and out of the 122 patients, 120 achieved SVR. Of those with SVR, 100% demonstrated extended virological response.

Conclusions: This study demonstrates that all patients who achieved SVR after DAA therapy maintained extended virological response. These findings underscore the durable effectiveness of DAA treatment in eradication of HCV and support its role in achieving long-term viral clearance.

Keywords: HCV, Extended Virological response, DAA, Durability

PE-63

Real-Life Experience of Sofosbuvir-Based Therapy and Glecaprevir/Pibrentasvir for HCV Infected Korean Patients: A Multicenter Cohort Study

Seong Hee Kang[1], Ji Won Kim[1], Hyung Joon Yim1, Tae Hyung Kim[2], Sun Young Yim[1], Eileen L Yoon[3], Young-Sun Lee[1], Dae Won Jun[3], Yeon Seok Seo[1], Ji Hoon Kim[1], Jong Eun Yeon[1], Kwan Soo Byun[1]

[1]Department of Internal Medicine, Korea University College of Medicine, Korea, [2]Department of Internal Medicine, Hallym University College of Medicine, Korea, [3]Department of Internal Medicine, Hanyang University College of Medicine, Korea

Aims: Sofosbuvir (SOF)-based therapy; SOF/RBV or Ledipasvir/SOF (LDV/SOF) and Glecaprevir/pibrentasvir (GLE/PIB) have been used in patients with hepatitis C virus (HCV) infection. This study aimed to compare the real-life effectiveness between SOF-based therapy and GLE/PIB treatment in genotype 1 (GT1) and 2 (GT2) HCV infection in Korea.

Methods: This multicenter, real-world, retrospective, cohort study consisted of 590 patients treated with a SOF-based regimen and GLE/PIB for a fixed 8- or 12-week duration from January 2014 to December 2022. The primary efficacy endpoint was sustained virologic response (SVR12).

Results: Among the treated patients, 134 had GT1 and 456 GT2 infections. The overall SVR12 rates in the per-protocol populations were 97.0% (130/134) for GT1 and 95.8% (437/456) for GT2. In GT 1 group, 78 received SOF-based treatment, while 56 received GLE/PIB treatment, and out of them, 36.9% of individuals had compensated cirrhosis. The SVR12 rate was similar between SOF-based and GLE/PIB therapy (96.2% vs. 98.2%; p=0.64). In the GT2 group, 351 individuals received SOF-based treatment, while 94 received GLE/PIB treatment. Among them, 123 patients (29.2%) had compensated cirrhosis, with 106 receiving SOF-based treatment and 17 receiving GLE/PIB treatment. The SVR12 rate was higher in GLE/PIB therapy than in SOF-based treatment (94.7% vs. 100%; p=0.01). In the sub-analysis based on cirrhosis, the SVR rate was higher in the GLE/PIB treatment group in patients without cirrhosis (95% vs. 100%; p=0.04). However, in patients with cirrhosis, both treatment groups showed similar efficacy.

Conclusions: In GT2, GLE/PIB therapy showed a higher tendency for SVR rates. However, both SOF-based and GLE/PIB therapy effectively treat GT1- and GT2-HCV-infected patients with high SVR12 rates.

Keywords: Chronic hepatitis C, Sofosbuvir, Glecaprevir/Pibrentasvir, Treatment

PE-64

Treatment Efficacy and Safety Profile of Sofosbuvir and Velpastavir Based Treatement in South Korea: Multi-Institutional Prospective Study

Jae Hyun Yoon[1], Ju Yeon Cho[2], Jin Dong Kim[3], Hun Gil Cho[4], Chang Hun Lee[5]

[1]Department of Gastroenterology and hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea, [2]Department of Internal Medicine, College of Medicine, Chosun University, Gwangju, Korea, [3]Department of Internal Medicine, Cheju Halla General Hospital, Jeju, Korea, [4]Department of Gastroenterology and hepatology, Wonkwang University Hospital and Medical School, Iksan, South Korea, [5]Department of Gastroenterology and hepatology, Jeonbuk National University Hospital and Medical School, Jeonju, South Korea

Aims: Sofosbuvir and velpatasvir (S/V) is a combination of direct-acting antiviral agents (DAA) which has strong treatment efficacy on all genotypes of hepatitis C virus (HCV) and S/V plus voxilaprevir (S/V/V) has also demonstrated good results in patients with treatment failure with other DAA agents. These two agents have been recently introduced in Korea and we elucidated the real-world treatment efficacy and safety profile in South Korea.

Methods: From November 2022 to May 2023, patients diagnosed as chronic HCV infection and underwent S/V based HCV treatment from five hospitals were enrolled. Total 62 patients were enrolled and 46 DAA treatment-naïve patients underwent 400mg of sofosbuvir and 100mg of velpatasvir medication for 12weeks and 16 patients took same dosage of S/V plus 100mg of voxilaprevir for 12 weeks.

Results: Among 46 patients with S/V, the mean age was 64.23 years, 20 (51.3%) patients were male. Eighteen patients (46.2%) had genotype 2, 21 patients (53.8%) had genotype 1b and only two patients had prior history of interferon treatment. The mean baseline level of HCV RNA was 3,753,531 IU/mL and each 4 and 6 patients had underlying decompensated liver cirrhosis and compensated liver cirrhosis, respectively. Due to lack of observation period, the end of treatment response and the sustained virological response at 12th week was assessable in 22 and 7 patients, respectively and all of the patients demonstrated undetectable HCV RNA at each time. Among 16 patients who underwent S/V/V regimen, the mean age was 61.84 years, 5 (31.3%) patients were male. All of the enrolled patients had genotype 1b HCV and the number of patients with previous DAA treatment history were as follows; daclatasvir and asunaprevir (11 patients), glecaprevir and pibrentasvir (4 patients), and elbasvir and grazoprevir (1 patients). Among enrolled patients, 11 patients had failed to achieve SVR with previous DAA treatment, 2 patients had achieved SVR and 1 patient had self-stopped the DAA. Four patients had underlying compensated liver cirrhosis. Due to lack of study period, the end of treatment response and the sustained virological response at 12th week was assessable in 12 and 6 patients, respectively and all of the patients demonstrated undetectable HCV RNA at each time. Both patients group in S/V and S/V/V had no serious adverse events (≥grade 3) during DAA treatment period.

Conclusions: S/V demonstrated excellent virological elimination of HCV and both S/V and S/V/V showed good safety profile.

Keywords: Sofosbuvir, Velpatasvir, Voxilaprevir, Efficacy, Safety

PE-65

HCV Elimination and Prevention of Opioid Overdose Mortality through a Needle Exchange Program

Marianne Alanko Blomé[1,2], Katja Troberg[3], Pernilla Isendahl[1], Martin Bråbäck[3], Sara Alsterberg[1], Anna Jerkeman[1]

[1]Department of Infectious Diseases, Skåne University Hospital, Malmö, Sweden, [2]Regional Office of Communicable Disease Prevention and Control, [3]Department of Addiction Medicine, Malmö, Sweden

Aims: For 25 years only two needle exchange programs (NEPs) were operational in Sweden (Lund since 1986, Malmö since 1987). They are run by the Infectious disease department at the Skåne University Hospital. During these 36 years, Malmö NEP (MNEP) has continuously evolved, keeping up with the needs of the target population. The current aim is to reduce morbidity and mortality related to Hepatitis C and opioid over doses.

Methods: MNEP has reached > 5200 persons, with 600 individuals conducting 6000 visits per year (75% male, age ≥ 18 years). MNEP provides sterile needles, syringes and paraphernalia and risk reduction counselling, medical care and psychosocial support. Baseline interviews on demographic facts and substance use completed with testing for HIV, hepatitis A (HAV), B (HBV) and C (HCV) and vaccinations against HAV and HBV are provided. A pilot study offering HCV-treatment on site (2018, n=50) with glecaprevir/pibrentasvir and Take Home Naloxone was introduced in 2018.

Results: HIV and HBV transmission has remained low. The previously high HCV prevalence (80% anti-HCV positivity) and incidence

(31,5/100 pyr in 1997-2005) has declined. The pilot study offering HCV-treatment found high rates of adherence (94%) and sustained virological clearance (90%), while 8 reinfections have been observed so far, equalling a rate of 9,5/100 person years at risk. The overall prevalence of HCV viremia has declined to around 16 %. Take home naloxone (THN) was introduced in 2018, expanding to all 4 NEPs and 30 OAT clinics in Skåne. To date, more than 10 000 doses of THN has been distributed and used in 800 OD situations.

Conclusions: A well-established Needle Syringe Program with ID expertise can constitute a solid platform for a holistic approach on health matters for its participants. Addressing both HCV and opioid overdoses is of great importance in reducing morbidity and mortality.

Keywords: HCV elimination, Opioid use disorder, People who inject drugs, Hepatitis C

PE-66

Metabolic Factors Influence the Efficacy of Direct Acting Antivirals against Chronic Hepatitis C on Liver Fibrosis

Tom Ryu[1], Jae Young Jang[1], Soung Won Jeong[1], Young Chang[1], Jeong-Ju Yoo[2], Sae Hwan Lee[3], Sang Gyune Kim[2], Young Seok Kim[2], Hong Soo Kim[3]

[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, [2]Department Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, [3]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan

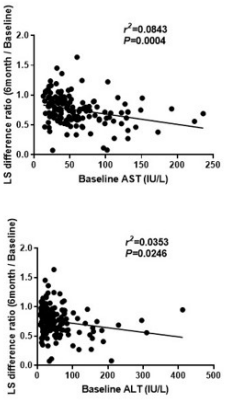
Aims: This study aims the influence of metabolic causes with using direct acting antivirals (DAA) against chronic heptitis C (CHC) regarding to the resolution of liver fibrosis and cirrhosis.

Methods: Patients (n=370) diagnosed with CHC in a training hospital between 2015 and 2022 were enrolled retrospectively with review of medical record. Liver stiffness were measured by FibroScan®, and the resolution of liver stiffness were checked by ratio (liver stiffness on 6 months after the DAA treatment / Baseline liver stiffness) and defined as 20% imrovement of measurement. Correlation was checked by Pearson correlation coefficient. Chi square test and logistic regression were used to conduct univariate and multivariate analysis, respectively. *P* value<0.05 was considered to statistically significant.

Results: Ratio of fibrosis measurements (6 months liver stiffness after DAA treatment / Baseline liver stiffness), which show lower level as a better efficacy for fibrosis, were significantly decreased with increase of serum baseline AST (r^2=0.0843, p<0.01) and ALT (r^2=0.0353, p=0.02) in the correlation graph. With univariate analysis, presence of type 2 diabetes [vs. normal, odds ratio (OR)=0.427 (0.181-1.008), p=0.048] and high level of serum low density lipoprotein (LDL) (≥ 130mg/dL) [vs. normal rage, OR=0.297 (0.102-0.871), p=0.022] had reduced probability of 20% imporvement of liver stiffness in 6 months after DAA treatment. In addition, multivariate analysis showed that high level of serum LDL [vs. normal range, OR=0.306 (0.103-0.906), p=0.033] would downregulate the probability of effective resolution of liver stiffness in 6 months after DAA treatment

Conclusions: Presence of type 2 diabetes and high level of serum LDL could be the inhibitory factor for fibrosis resolution in 6 months DAA treatment of CHC.

Figures and Table



Factors associated with 20% improvement of liver stiffness in 6 months

Characteristics	Univariate analysis		Multivariate analysis	
	OR [95% CI]	p value	OR [95% CI]	p value
Male gender (vs female)	1.349 [0.697-2.610]	0.373		
Hypertension (yes vs no)	1.420 [0.660-3.058]	0.446		
Diabetes Mellitus (yes vs no)	0.427* [0.181-1.008]	0.048	0.462 [0.136-1.566]	0.215
Significant alcohol consumption (yes or no)	3.278 [0.683-15.731]	0.119		
Obesity (BMI ≥ 25 kg/m2, yes or no)	0.926 [0.443-1.937]	0.838		
Age (Age ≥65 years or not)	1.079 [0.531-2.191]	0.834		
DAA regimen (Glecaprevir/Pibrentasvir or not)	0.624 [0.302-1.287]	0.200		
US based fatty liver (yes or no)	1.947 [0.826-4.589]	0.124		
US based liver cirrhosis (yes or no)	3.648* [1.637-8.129]	0.001	1.379 [0.416-4.567]	0.599
AST abnormality (AST ≥ 40 IU/L or not)	3.925* [1.953-7.890]	0.001	2.316 [0.981-5.465]	0.055
ALT abnormality (ALT ≥ 40 IU/L or not)	2.195* [1.108-4.348]	0.023	1.464 [0.491-4.360]	0.555
Serum albumin (Albumin ≥ 3.5 mg/dL or not)	1.446 [0.282-7.428]	0.657		
Serum LDL (LDL ≥ 130mg/dL or not)	0.297* [0.102-0.871]	0.022	0.306* [0.103-0.906]	0.033

Keywords: Chronic hepatitis C, Direct acting antivirals, Metabolism, Liver fibrosis

PE-67

Prognostic Factors of Post-Sustained Virological Response Outcome in Patients with Chronic Hepatitis C treated with Direct-Acting Antivirals

Won Sohn[1], Soo Young Park[2], Tae Hee Lee[3], Young Eun Chon[4], In Hee Kim[5], Byung-Seok Lee[6], Ki Tae Yoon[7], Jae Young Jang[8], Yu Rim Lee[9], Su Jong Yu[10], Won-Mook Choi[11], Sang Gyune Kim[12], Dae Won Jun[13], Joonho Jeong[14], Ji Hoon Kim[15], Eun Sun Jang[16], Hwi Young Kim[17], Sung Bum Cho[18], Byoung Kuk Jang[19], Jung-Gil Park[20], Jin-Woo Lee[21], Yeon Seok Seo[22], Jung Il Lee[23], Do Seon Song[24], Moon Young Kim[25], Hyung Joon Yim[26], Dong Hyun Sinn[27], Sang Hoon Ahn[28,29], Young Seok Kim[12], Heejoon Jang[30], Won Kim[30], Seungbong Han[31], Seung Up Kim[28,29]

[1]Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea; 2Kyungpook National University Hospital, Kyungpook National University, Daegu, Korea; [3]Konyang University College of Medicine, Daejeon, Korea; [4]CHA Bundang Medical Center, CHA University, Seongnam, Korea; [5]Chonbuk National University Hospital, Chonbuk National University Medical School, Jeonju, Korea; [6]Chungnam National University School of Medicine, Daejeon, Korea; [7]Pusan National University Yangsan Hospital, Pusan National, Yangsan, Korea; [8]Soonchunhyang University College of Medicine, Seoul, Korea; [9]Kyungpook National University Chilgok Hospital, Kyungpook National University, Daegu, Korea; [10]Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [11]Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [12]Soonchunhyang University College of Medicine, Bucheon, Korea; [13]Hanyang University College of Medicine, Seoul, Korea; [14]Ulsan University Hospital, Ulsan University College of Medicine, Ulsan, Korea; [15]Guro Hospital, Korea University College of Medicine, Seoul, Korea; [16]Seoul National University Bundang Hospital, Seongnam, Korea; [17]College of Medicine, Ewha Womans University, Seoul, Korea; [18]Chonnam National University Hospital, Chonnam National University, Hwasun Korea; [19]Keimyung University School of Medicine, Daegu, Korea; [20]College of Medicine, Yeungnam University, Daegu, Korea; [21]Inha University Hospital, Inha University School of Medicine, Incheon, Korea; [22]Korea University Anam Hospital, Korea University Medical College, Seoul, Korea; [23]Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [24]St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea; [25]Yonsei University Wonju College of Medicine, Wonju, Korea; [26]Korea University Ansan Hospital, Ansan, Korea; [27]Samsung Medical Center, Sungkyunkwan University School of

Medicine, Seoul, Korea; [28]Yonsei University College of Medicine, Seoul, Korea; [29]Yonsei Liver Center, Severance Hospital, Seoul, Korea; [30]Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea; [31]Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea

Aims: Direct-acting antivirals (DAAs) improve the prognosis of patients with chronic hepatitis C (CHC). This study investigated whether DAA treatment improves the disease burden in patients with CHC using individual participant data.

Methods: This nationwide, multicentre, retrospective cohort study recruited patients with CHC from 29 tertiary academic institutes in South Korea. The primary outcome was disease burden, reflected by disability-adjusted life years (DALYs). Improvement of fibrotic burden after DAA treatment was assessed using APRI score, FIB-4 index, and liver stiffness (LS) by transient elastography. The clinical outcomes were hepatocellular carcinoma (HCC), decompensation, or mortality.

Results: Between January 2007 and December 2022, data from 11,726 patients with CHC, including 8,464 (72%) treated with DAAs, were analyzed. DAA treatment significantly improved ARRI-, FIB-4-, and LS-based fibrotic burden (all $p<0.001$). During the follow-up (median 27.5 months), 469 patients died, 586 developed HCC, 580 developed decompensation, and 18 underwent liver transplantation. The APRI-based DALY estimate was significantly lower in the DAA group than in the untreated group (mean 5.0 vs. 5.9 years, $p<0.001$), as was the FIB-4-based DALY estimate (mean 5.7 vs. 6.3 years, $p<0.001$). The difference between the two groups with respect to APRI- and FIB-4-based DALYs was highest in patients 40–60 years of age. In multivariable analyses, DAA group had significantly reduced risk of HCC, decompensation, and mortality, compared to the untreated group (hazard ratio=0.47, 0.31, and 0.22, respectively; all $p<0.001$).

Conclusions: DAA treatment significantly improved the clinical outcomes and reduced the disease burden in patients with CHC.

Keywords: Hepatitis C, Prognosis, Post-SVR

PE-68

Cascade of Care for Chronic Hepatitis C in South Korea

Sang Bong Ahn[1], Dae Won Jun[2], Joo Hyun Oh[1], Eileen Yoon[2]

[1]Nowon Eulji Medical Center, Eulji University, [2]Hanyang University College of Medicine

Aims: The World Health Organization has set ambitious targets for the elimination of hepatitis C virus (HCV) by 2030, aiming to diagnose 90% of people with HCV and treat 80% of those diagnosed. However, significant barriers hinder progress in accessing affordable HCV testing, direct-acting antiviral (DAA) treatment, and effective patient linkage to HCV care. The HCV care cascade plays a crucial role in improving treatment rates. This study aims to examine the cascade of care for chronic hepatitis C patients in South Korea and identify factors impeding treatment.

Methods: We conducted an analysis using data from the Korea Disease Control and Prevention Agency, which registered 8,810 patients with chronic hepatitis C in 2019. We collected and analyzed baseline characteristics, income levels, healthcare facility utilization, actual treatment status, comorbidities, and laboratory test results.

Results: The proportions of patients diagnosed at primary, secondary, and tertiary healthcare facilities were 26%, 53%, and 21%, respectively. Among all diagnosed patients, 41% did not receive actual treatment. Treatment rates were 11.5% at primary healthcare facilities and 47.3% and 59.4% at secondary and tertiary healthcare facilities, respectively, for patients diagnosed at these respective levels. Among patients diagnosed at primary healthcare facilities, 60% were referred to higher-level facilities, and 80% of those referred received treatment. Treatment rates did not significantly differ by region, but the lowest income group (below 25%) exhibited lower treatment rates. However, income level did not show a proportional relationship with treatment rates. Treatment rates were also lower for elderly patients, those with underlying comorbidity, and patients with liver cirrhosis.

Conclusions: Treatment uptake for chronic hepatitis C in South Korea falls below optimal levels, posing a challenge to achieving the goal of HCV elimination. Efforts are needed to address barriers that reduce treatment rates and improve the cascade of care for HCV patients.

Keywords: Chronic hepatitis C, Cascade of care

PE-69

Clinical Characteristics and Treatment Outcomes of Patients with Hepatitis C Virus and Human Immunodeficiency Virus Coinfection in Korea: A Retrospective Multicenter Study

Jae Yoon Jeong[1], Taewan Ju[1], Su Jong Yu[2], Jeong Won Jang[3], Soon Sun Kim[4], Jae Hyun Yoon[5], Hyuk Soo Eun[6], Jonggi Choi[7], Ki Tae Yoon[8], Young Kul Jung[9], Soo Young Park[10], Geum-Youn Gwak[11], Tae Yeob Kim[12], Do Young Kim[13], Ji Hoon Kim[14], Jin-Woo Lee[15].

[1]Department of Internal Medicine, National Medical Center, Seoul, [2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, [3]Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [4]Department of Internal Medicine, Ajou University School of Medicine, Suwon, [5]Department of Internal Medicine, Chonnam National University Hospital and College of Medicine, Gwangju, [6]Department of Internal Medicine, Chungnam National University Hospital, Daejeon, [7]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [8]Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, [9]Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, [10]Department of Internal Medicine, Kyungpook National University School of Medicine, Daegu, [11]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [12]New Hope Internal Medicine Clinic, Seoul, [13]Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, [14]Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, [15]Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, Korea

Aims: Because of the very low incidence of human immunodeficiency virus (HIV) infection in Korea, the epidemiologic data on hepatitis C virus (HCV)/HIV coinfection are limited. We investigated the clinical characteristics and treatment outcomes of patients with HCV/HIV coinfection in Korea.

Methods: We collected retrospectively data of patients diagnosed with HCV/HIV coinfection at 12 academic hospitals in Korea from

2009 to 2020.

Results: A total of 125 patients were included. Male gender was predominant (n=114, 91.2%), and the mean age was 46.5±13.4 years. Of them, 12 patients (9.6%) had cirrhosis and 7 (5.6%) were positive HBsAg. During follow up, 2 patients (1.6%) developed hepatocellular carcinoma and 9 (7.2%) died. Among the 113 patients (90.4%) who underwent HCV genotype test, most were genotype 2 (n=53, 46.9%) and genotype 1b (n=42, 37.2%). In particular, genotype 1a was 12.4% (n=14). Ninety patients (72%) were treated with antiviral agents and a total of 105 antiviral treatments were administered. The sustained virologic response rate of the patients receiving direct acting antivirals (DAAs) treatment was greater than of those receiving pegylated interferon-based treatment (89.2% vs 58.1%, $p<0.001$).

Conclusions: The patients with HCV/HIV coinfection in Korea had high proportion of men and incidence of genotype 1a. They showed a better treatment response to DAAs treatment than to interferon-based treatment.

Keywords: Hepatitis C virus, Human immunodeficiency Virus, Korea

PE-70

The Risk of Hepatocellular Carcinoma Depending on Liver Cirrhosis in Patients with Chronic Hepatitis C: A National Cohort Study

Jong-In Chang[1], Gi Hyeon Seo[2], Eunju Kim[1], Young Youn Cho[1], Hyung Joon Kim[1]

[1]Department of Internal Medicine, Chung-Ang University College of medicine, Seoul, Korea, [2]Health Insurance Review and Assessment of Service, Seoul, Korea

Aims: Current direct-acting antiviral (DAA) treatments for the hepatitis C virus achieve high rates of sustained virological response, thus improving clinical outcomes. Chronic hepatitis C patients are at-risk for hepatocellular carcinoma (HCC) even after DAA treatment. Limited national data exist on the long-term clinical course of DAA use and whether surveillance is needed depending on liver cirrhosis in Korean patients with chronic hepatitis C.

Methods: This is a population-based retrospective cohort study using the database of the Health Insurance Review and Assessment Service in Korea. A total of 16,344 adult patients who were newly administered Ledipasvir/sofosbuvir or Glecaprevir/pibrentasvir between 2016 and 2021 without a previous history of HCC were included in the analysis. The primary outcome was the incidence of HCC after DAA treatment in patients with and without cirrhosis. The secondary outcome was whether there were differences in HCC incidence by gender and age group.

Results: The average age of 16,344 patients was 59.4 years, males were 46.9%, the average follow-up period was 23.5 months, and 2,928 (17.9%) patients had liver cirrhosis. The incidence of HCC per 1,000 patient-years was 9.38 in all patients, 3.68 in non-cirrhotic patients, and 33.17 in cirrhotic patients. In both patients with and without cirrhosis, age ≥65 and male gender were associated with the incidence of HCC in each subgroup.

Conclusions: Even after DAA treatment, the risk of HCC remains high in patients with chronic hepatitis C with cirrhosis, whereas the risk is significantly lower in patients without cirrhosis. These results may support the argument that DAA treatment is important before cirrhosis in patients with chronic hepatitis C and that HCC surveillance is necessary continuously after DAA treatment in patients with cirrhosis.

Keywords: Chronic hepatitis C, Liver cirrhosis, Direct-acting antivirals, Hepatocellular carcinoma

PE-71

Impact of HCV Eradication on Symptoms of Extrahepatic Manifestations in Patients with Type 2 Diabetes Mellitus Treated with SOF/VEL

Chung-Feng Huang[2,3], Chi-Yi Chen[45*], Chao-Hung Hung[4], Hsing-Tao Kuo[8], Chi-Ming Tai[5,6], Lein-Ray Mo[7], Kuo-Chih Tseng[10,11], Ching-Chu Lo[12], Ming-Jong Bair[13,14], Szu-Jen Wang[15], Jee-Fu Huang[2,3], Ming-Lun Yeh[2,3], Chun-Ting Chen[16,17], Ming-Chang Tsai[18], Chien-Wei Huang[19], Pei-Lun Lee[20], Tzeng-Hue Yang[21], Yi-Hsiang Huang[22,23], Lee-Won Chong[24,25], Chien-Lin Chen[26], Chi-Chieh Yang[27], Chao-Hung Hung[4], Sheng-Shun Yang[28], Pin-Nan Cheng[29], Tsai-Yuan Hsieh[16], Jui-Ting Hu[30], Wen-Chih Wu[31], Chien-Yu Cheng[32], Guei-Ying Chen[33], Guo-Xiong Zhou[34], Wei-Lun Tsai[35], Chien-Neng Kao[36], Chih-Lang Lin[37], Chia-Chi Wang[38], Ta-Ya Lin[39], Chih-Lin Lin[40], Wei-Wen Su[41], Tzong-Hsi Lee[42], Te-Sheng Chang[43], Chun-Jen Liu[44], Chia-Yen Dai[2,3], Cheng-Yuan Peng[46,47], Jia-Horng Kao[44], Han-Chieh Lin[22,23], Wan-Long Chuang[2,3], Ming-Lung Yu[1–4*] (TACR study group)

[1]School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan, [2]Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [3]Hepatitis Research Center, College of Medicine and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan, [4]Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan, [6]School of Medicine for International Students, College of Medicine, I-Shou University, Kaohsiung, Taiwan, [7]Division of Gastroenterology, Tainan Municipal Hospital (Managed By Show Chwan Medical Care Corporation), Tainan, Taiwan, [8]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi Mei Medical Center, Yongkang District, Tainan, Taiwan, [9]Ph.D. Program in Translational Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, and Academia Sinica, Taiwan, [10]Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chiayi, Taiwan, [11]School of Medicine, Tzuchi University, Hualien, Taiwan, [12]Division of Gastroenterology, Department of Internal Medicine, St. Martin De Porres Hospital, Chiayi, Taiwan, [13]Division of Gastroenterology, Department of Internal Medicine, Taitung Mackay Memorial Hospital, Taitung, Taiwan, [14]Mackay Medical College, New Taipei City, Taiwan, [15]Division of Gastroenterology, Department of Internal Medicine, Yuan's General Hospital, Kaohsiung, Taiwan, [16]Division of Gastroenterology, Department of Internal Medicine, TriService General Hospital, National Defense Medical Center, Taipei, Taiwan, [17]Division of Gastroenterology, Department of Internal Medicine, TriService General Hospital Penghu Branch, National Defense Medical Center, Taipei, Taiwan, [18]School of Medicine, Chung Shan Medical University, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan, [19]Division of Gastroenterology, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan, [20]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi Mei Medical Center, Liouying, Tainan, Taiwan, [21]Lotung Poh-Ai Hospital, Yilan, Taiwan, [22]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, [23]Institute of Clinical Medicine, School of Medicine,

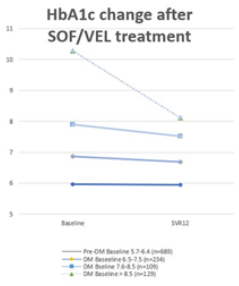
National Yang-Ming Chiao Tung University, Taipei, Taiwan, [24]Division of Hepatology and Gastroenterology, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, [25]School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan, [26]Department of Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and Tzu Chi University, Hualien, Taiwan, [27]Department of Gastroenterology, Division of Internal Medicine, Show Chwan Memorial Hospital, Changhua, Taiwan, [28]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, [29]Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [30]Liver Center, Cathay General Hospital, Taipei, Taiwan, [31]Wen-Chih Wu Clinic, Fengshan, Kaohsiung, Taiwan, [32]Division of Infectious Diseases, Department of Internal Medicine, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan, [33]Penghu Hospital, Ministry of Health and Welfare, Penghu, Taiwan, [34]Zhou Guoxiong Clinic, Penghu, Taiwan, [35]Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [36]National Taiwan University Hospital Hsin-Chu Branch, Hsinchu, Taiwan, [37]Liver Research Unit, Department of Hepato-Gastroenterology and Community Medicine Research Center, Chang Gung Memorial Hospital at Keelung, College of Medicine, Chang Gung University, Keelung, Taiwan, [38]Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation and School of Medicine, Tzu Chi University, Taipei, Taiwan, [39]Cishan Hospital, Ministry of Health and Welfare, Kaohsiung, Taiwan, [40]Department of Gastroenterology, Renai Branch, Taipei City Hospital, Taipei, Taiwan, [41]Department of Gastroenterology and Hepatology, Changhua Christian Hospital, Changhua, Taiwan, [42]Division of Gastroenterology and Hepatology, Far Eastern Memorial Hospital, New Taipei City, Taiwan, [43]Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan and College of Medicine, Chang Gung University, Taoyuan, Taiwan, [44]Hepatitis Research Center and Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [45]Division of Gastroenterology and Hepatology, Department of Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan, [46]Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan

Aims: Type 2 diabetes mellitus (T2DM) is considered an extrahepatic manifestation of chronic hepatitis C (CHC). Studies have shown early identification and treatment of CHC in T2DM may reduce diabetic complications through improved glycemic control.
The goal of this study was to investigate whether eradication of HCV infection with SOF/VEL is associated with improved glycemic control and renal function in patients with T2DM using TACR database.

Methods: This is a retrospective analysis of adult patients cured with SOF/VEL from Aug 2019 to Dec 2022. Patients with SVR results, HbA1c at baseline and SVR 12, without use of ribavirin, or without prior DAA treatment were included in this analysis. Change in HbA1c levels were assessed at treatment baseline and SVR 12.

Results: 9,187 patients received SOF/VEL were reviewed, of which 2,180 patients met inclusion criteria, 2,162 achieved SVR12. 695 patients with T2DM (DM group) and 1,485 patients without T2DM (non-DM group) were included in this analysis. HbA1c were significantly decreased from 7.32±1.72% at baseline to 6.87±1.34% at SVR in DM group (p<0.001); while no HbA1c change was observed in non-DM. The mean decrease of HbA1c were 0.02±0.59, 0.17±0.74, 0.37±1.20, 2.17±2.09 in baseline HbA1c of 5.7-6.4, 6.5-7.5, 7.6-8.5 and > 8.5. The decrease of HbA1c were higher in DM with cirrhosis than without cirrhosis (0.62±1.76 vs. 0.41±1.43). 117/472 patients with baseline A1c ≥ 6.5 had A1c improved to <6.5 at SVR 12. 170/689 Pre-DM patients (with baseline A1c 5.7-6.4) had A1c improved to <5.7 at SVR 12. eGFR of DM patients remains stable and significant improvement of FIB 4 and albumin were observed.

Conclusions: Eradication of HCV with SOF/VEL resulted in a significant decrease in HbA1c, particularly in DM patients with a high pretreatment HbA1c. This study suggests treating HCV improves symptoms of both hepatic and extrahepatic manifestations and should motivate non-GI-hepatology specialties to engage in HCV care.



	HbA1c	N	BL	SVR12	A1c change	P value
Non-DM	< 5.7	1,019	5.26±0.32	5.34±0.50	0.08±0.43	<0.001*
Pre DM	5.7-6.4	689	5.97±0.22	5.94±0.61	-0.02±0.59	0.313
DM	6.5-7.5	234	6.86±0.26	6.69±0.79	-0.17±0.74	0.001*
	7.6-8.5	109	7.90±0.26	7.52±1.17	-0.37±1.20	0.002*
	> 8.5	129	10.28±1.51	8.12±1.66	-2.17±2.09	<0.001*

	SVR 12 A1c				
Baseline A1c	> 8.5	7.6-8.5	6.5-7.5	5.7-6.4	< 5.7
> 8.5 (n=129)	44	39	21	19	6
7.6-8.5 (n=109)	22	19	58	9	1
6.5-7.5 (n=234)	7	23	122	71	11
5.7-6.4 (n=689)	4	4	51	460	170

Keywords: HCV, Extrahepatic manifestation, Diabetes mellitus, HbA1c

PE-72

Hepatoprotective Effects of Temulawak Rhizome in the Study of Liver Disease in Hepatitis C

Andi Nursanti, Haryanto

Wallace University, Indonesia

Aims: Temulawak is one type of plant native to Indonesia and is quite popularly used in its root part in the traditional treatment of hepatic diseases. One of the hepatic diseases is hepatitis c caused by the HBV virus so substances that can inhibit HBV gene expression and replication using hepatoprotective substances are needed. This study aims to describe Temulawak phytochemicals that have hepatoprotective effects against the hepatitis c virus.

Methods: This study uses qualitative and quantitative research with ADS methods derived from secondary data on temulawak, hepatitis c, and hepatoprotective effects. The research subjects in the hepatoprotective effect were male Sprague Dawley rats, 3-4 months old, weighing 150-200 grams made in 5 groups.

Results: Phytochemical results show that Temulawak contains polyphenol and flavonoid compounds in the form of curcuminoids and curcumin analogs including demetoxycurcumin, bisdemethoxycurcumin. There are essential oils consisting of d-camfer, cyclo isoren, mirsen, tumerol, xanthorrhizol, zingiberen, zingeberol. The hepatoprotective activity of temulawak can be caused by free radical capture and antioxidant activity resulting from the presence of polyphenol and flavanoid compounds and other substances in the temulawak rhizome. Curcumin can also increase glutathione S-transferase (GST), and inhibit several proinflammatory factors such as nuclear factor-κB (NF-kB) and profibrotic cytokines so that inflammatory by-products are reduced. The research on animal models showed that rats given temulawak rhizome decoction induced by aspirin decreased levels with a dose of 2.6 g/kgBB and 5.2 g/kgBB liver damage. Other clinical results showed that curcumin at high doses (1000-2000 mg/day) did not produce harmful effects on the body

Conclusions: Temulawak rhizome with phytochemical content of

polyphenols, flavonoids, and other substances has a hepatoprotective effect so that it can be used as an alternative hepatoprotection in Hepatitis C patients.

Keywords: Hepatitis C, Phytochemicals, Temulawak rhizome

PE-73

Addition of Neutrophil-to-Lymphocyte Ratio to Pre-DAA FIB-4 to Predict De Novo Liver Complications in Hepatitis C

Chun-Ming Hong[1], Tung-Hung Su[2], Shih-Jer Hsu[2], Tai-Chung Tseng[3], Chen-Hua Liu[2], Hung-Chih Yang[2], Jia-Horng Kao[2,4], Pei-Jer Chen[2,4], Pin-Nan Cheng[5], Chao-Hung Hung[6,7], Cheng-Yuan Peng[8], Chien-Hung Chen[9], Chun-Yen Lin[10], Hsing-Tao Kuo[11], Han-Chieh Lin[12], Yi-Hsiang Huang[12], Chi-Yi Chen[13], Chih-Lin Lin[14], Pei-Chien Tsai[15], Yu-Syuan Zeng[15], Chia-Yen Dai[15], Wan-Long Chuang[15], Jee-Fu Huang[15], Chung-Feng Huang[15], Ming-Lun Yeh[15], Ming-Lung Yu[15], Chun-Jen Liu[2]

[1]Division of Hospital Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [2]Division of Gastroenterology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [3]Department of Medicine Research, National Taiwan University, Taipei, Taiwan, [4]Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan, [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, [6]Division of Hepatogastroenterology, Department of Internal Medicine, ChiaYi Chang Gung Memorial Hospital, Taiwan, [7]Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan, [8]Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital; School of Medicine, China Medical University, Taichung, Taiwan, [9]Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan, [10]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Branch, Taiwan, [11]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chi Mei Medical Center, Taiwan, [12]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, [13]Division of Gastroenterology and Hepatology, Department of Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Taiwan, [14]Department of Gastroenterology, Renai Branch, Taipei City Hospital, Taipei, Taiwan, [15]Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Aims: Direct-acting antiviral agents (DAAs) are able to achieve high sustained virologic response (SVR) in chronic hepatitis C (CHC) patients; yet a proportion of patients still experience *de novo* liver complications after SVR. Identification of risk factors is clinically important.FIB-4 index is a useful noninvasive tool to assess fibrosis, while neutrophil-to-lymphocyte ratio (NLR) is a biomarker for systemic inflammation. Our study aimed to investigate whether the addition of NLR can increase the prediction power of pre-DAA FIB-4 for *de novo* liver complications after SVR.

Methods: We recruited patients via the platforms of The Taiwan HCV Registry and National Health Insurance Registry Database. The inclusion criteria were patients who achieved SVR12 after DAA therapy and were followed for at least 24 months after SVR12. Liver complications included ascites, hepatic encephalopathy, variceal bleeding, and HCC.

Results: Totally 7657 patients were recruited from 2013 to 2018. Among them, 3674 patients (48.0%) had a FIB-4 value > 3.25 and 491 patients (6.4%) had a NLR > 4 before DAA. After two-year of follow-up after SVR 12, 214 patients (2.8%) developed de novo liver complications. Factors associated with the development of liver complications included male gender, diabetes mellitus, hyperlipidemia, chronic kidney disease, and pre-DAA FIB-4 >3.25 in multivariate analyses.

Conclusions: The overall incidence of *de novo* liver-associated complications after SVR is low during short-term follow-up. Elevated pre-DAA FIB-4 is associated with *de novo* liver complications after SVR, whereas the addition of pre-DAA NLR does not increase the prediction power.

Keywords: Direct-acting antiviral agent, Chronic hepatitis C, Sustained virologic response

[Hepatitis C: Clinical Aspects: Non-Therapy]

PE-74

Association between Hepatitis C, Autoimmune Hepatitis and Insulin Resistance

Javad Alizargar

NTUNHS, Iran

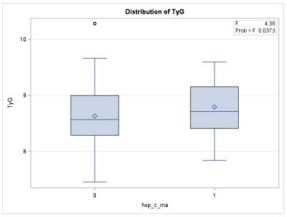
Aims: One of the pathogenic characteristics in individuals with HCV infection is insulin resistance, which frequently triggers the onset of type -2 diabetes. Insulin resistance is a significant factor in the emergence of numerous HCV infection-related problems. Hepatitis C increases insulin resistance, which in turn causes interferon resistance, the advancement of steatosis, and fibrosis. Increased insulin resistance is frequently associated with chronic liver disease. In this study we are trying to evaluate the status of insulin resistance calculated by a new marker, TyG (triglyceride glucose index) in National Health and Nutrition Examination Survey database in hepatitis C and autoimmune hepatitis patients. Viral hepatitis will be also compared with autoimmune hepatitis regarding the insulin resistance.

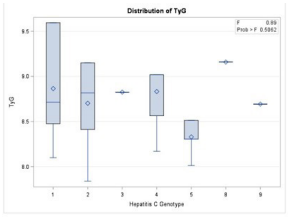
Methods: National Health and Nutrition Examination Survey database was used to extract the database. Demographic characteristics and the status of hepatitis C infection based on RNA test, also genotypes of hepatitis C and autoimmune hepatitis status were extracted from the database, and data was analyzed using ANOVA, Spearman's rank correlation and logistic regression because of the non-normality of their distributions.

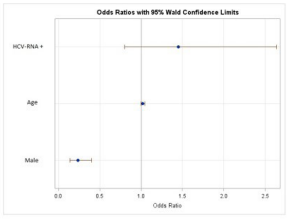
Results: insulin resistance is higher in hepatitis C patients confirmed with hepatitis C RNA (HCV-RNA), but not different between different Hepatitis C genotypes. Correlation analysis with Spearman's rank correlation showed no correlation between hepatitis C infection and insulin resistance. Although increasing the risk of infection, after controlling for age and gender, insulin resistance cannot be associated with hepatitis C infection (OR=1.451, CI=0.798-2.638). Compared to the viral hepatitis, autoimmune hepatitis patients have higher insulin resistance and insulin resistance is highly associated with autoimmune hepatitis (OR=11.06, CI=2.163-56.551).

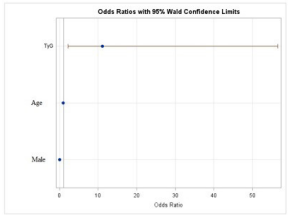
Conclusions: Hepatitis C patients have high insulin resistance levels but Hepatitis C infection is not independently associated high insulin

resistance. On the other hand, Insulin resistance is highly and independently associated with autoimmune hepatitis.









Keywords: Hepatitis C, HCV-RNA, Insulin resistance, Viral hepatitis

PE-75

Risk of Hepatitis C Virus Transmission through Acupuncture: A Systematic Review and Meta-Analysis

Hyun Yang[1], Myung Han Hyun[2], Jihyun An[3]

[1]Division of Hepatology, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, Catholic University College of Medicine, Republic of Korea, [2]Division of Hematology-Oncology, Department of Internal Medicine, Korea University Medical Center, Korea University College of Medicine, Seoul, Republic of Korea, [3]Department of Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Gyeonggi, Republic of Korea

Aims: Chronic hepatitis C is a major risk factor for liver cirrhosis, hepatocellular carcinoma, and hepatic failure. Although traditional practices, including acupuncture, may increase the risk of hepatitis C virus (HCV) infection, the association remains controversial. Therefore, we performed a meta-analysis evaluating the risks of acupuncture and hepatitis C transmission.

Methods: Two researchers independently screened studies from the databases from inception to May 12, 2022. Baseline demographics, including study design, ethnicity, publication year, enrollment period, study participants, HCV transmission odds ratio (OR), and 95% confidence intervals were extracted, pooled, and analyzed using random-effect models. Subgroup analyses utilizing study design and ethnicity were performed. Heterogeneity and publication bias were analyzed using the Higgins I^2 test and funnel plots, respectively.

Results: Finally, 28 studies with 194,826 participants (178,583 controls [91.7%] vs 16,243 acupuncture users [8.3%]) were enrolled. The pooled analysis showed that acupuncture users had a significantly higher HCV transmission rate than controls with heterogeneity (OR, 1.84 [1.46-2.32]; p<0.001; I^2=80%). In the subgroup analysis, both cross-sectional case-control (n=14; OR, 1.96 [1.47-2.61]; p<0.001; I^2=88%) and cross-sectional studies (n=12; OR, 1.85 [1.32-2.61]; p<0.001; I^2=0%) showed significantly higher HCV infection rates in the acupuncture group than in the control group. Both Asian and non-Asian populations showed a higher HCV transmission risk in acupuncture users than in the controls (all Ps<0.001). No significant publication bias was observed.

Conclusions: Our findings suggest that acupuncture can increase HCV transmission. Due to HCV's contagiousness, unsafe medical and social practices, including acupuncture, should be performed with caution.

Keywords: HCV, Acupuncture, Transmission risk

PE-76

Interim Results of an Automated Electronic Medical Record-Based Alert System for The Micro-Elimination of Hepatitis C-A Single Center-Based Experience

Hee Yeon Kim, Sung Won Lee, Jung Hyun Kwon, Chang Wook Kim, Se Hyun Cho, Hee Chul Nam, Hyun Yang, Keungmo Yang, Do Seon Song, U Im Chang, Jin Mo Yang, Hae Lim Lee, Soon Woo Nam, Soon Kyu Lee, Seok-Hwan Kim, Myeong Jun Song, Pil Soo Sung, Ji Won Han, Jeong Won Jang, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

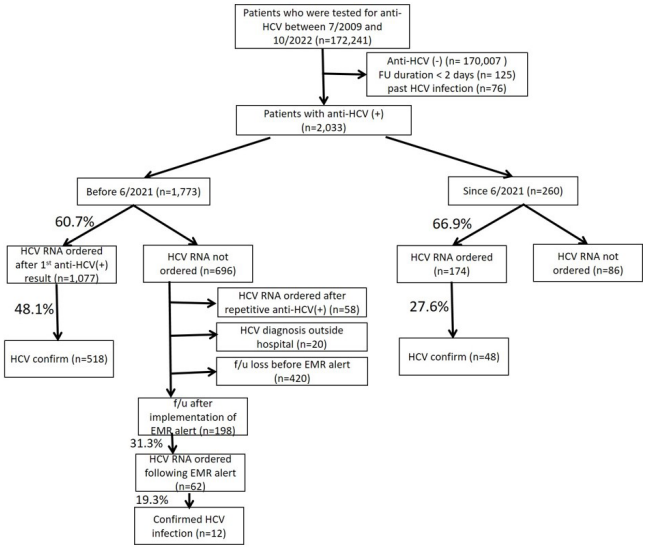
Aims: The diagnostic process and linkage to care continue to represent the primary obstacles impeding the micro-elimination of the hepatitis C virus (HCV). This study aimed to evaluate the effectiveness of integrating an automated electronic medical record (EMR)-based alert system in a tertiary referral center.

Methods: The analysis included 2,234 patients who tested positive for HCV antibodies between July 2009 and October 2022. Starting from June 2021, an EMR-based alert system was implemented to remind physicians to conduct HCV RNA testing for patients with a history of positive HCV tests but no confirmatory HCV RNA test or recent positive HCV test result.

Results: Out of the 172,241 patients who underwent anti-HCV testing during the study period, 2,234 patients (1.3%) tested positive for anti-HCV. After excluding patients previously diagnosed with HCV and those with a follow-up duration of less than 2 days, 2,033 patients were included in the analysis. Before the introduction of the automated EMR-based alert system, 60.7% (1077/1773) of the patients underwent HCV RNA testing following the initial positive anti-HCV result. Among them, 48.1% (518/1077) were confirmed to have HCV infection. Among the patients who did not undergo the HCV RNA confirmatory test following the initial positive anti-HCV result, 58 patients received the HCV RNA test after repetitive positive anti-HCV results. Notably, 3.1% (20/638) of patients who did not undergo the HCV RNA confirmatory test within our hospital were diagnosed with HCV elsewhere. Among 198 patients who had not undergone HCV RNA test before EMR-based alert system and had been followed up after alert system, 31.3% (62/198) were tested following the alert notification, resulting in confirmation of 12 new HCV infections. After incorporating an EMR-based alert system, 66.9% (174/260) of anti-HCV-positive patients were ordered an HCV RNA test, with 27.6% (48/174) confirmed cases.

Conclusions: The integration of an EMR-based alert system for HCV microelimination improved RNA testing rates in new anti-HCV positive patients and diagnosis of previously missed HCV infection in a hospital-based setting. However, further modification and promotion of EMR-based alert system is needed to enhance HCV confirmation rates.

Keywords: Hepatitis C, Microelimination, Alert system



PE-77

HCC Prediction Models Effectively Assess the Risk of HCC in Chronic Hepatitis C Patients without Advanced Fibrosis after Oral Antiviral Therapy: A Multicenter Study

Yu Rim Lee[1†], Hyun Young Woo[2†], Jung Gil Park[3], Min Kyu Kang[3], Jaeyoung Jang[1], Jeong Eun Song[4], Byoung Kuk Jang[5], Young Oh Kweon[1], Won Young Tak[1], Se Young Jang[1], Changhyeong Lee[4], Byung Seok Kim[4], Jae Seok Hwang[5], Woo Jin Chung[5], Jeong Ill Suh[6], Jeong Heo[2], Nae-Yun Heo[7], Seung Ha Park[7], Jun Sik Yoon[8], Joonho Jeong[9], Sang Gyu Kwak[10], Yang Hyun Baek[11*], Soo Young Park[1*]

[1]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea; [2]Department of Internal Medicine, College of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, Busan, South Korea; [3]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, South Korea; [4]Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, South Korea; [5]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea; [6]Department of Internal Medicine, Dongguk University Gyeongju Hospital, Dongguk University College of Medicine, Gyeongju, South Korea; [7]Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea; [8]Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea; [9]Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, South Korea; [10]Department of Medical Statistics, Daegu Catholic University School of Medicine, Daegu, South Korea; [11]Department of Internal Medicine, Dong-A University Hospital, Busan, South Korea

Aims: The current guidelines recommend lifelong ultrasound surveillance for chronic hepatitis C patients with advanced fibrosis or cirrhosis after achieving SVR with DAA therapy. However, there are limited studies on the risk of HCC in patients without advanced fibrosis. Therefore, we aimed to identify high risk group for HCC development using HCC prediction models.

Methods: This study included 1,839 chronic hepatitis C patients without advanced chronic liver disease from 10 tertiary hospitals who were treated with DAA. Advanced fibrosis was defined as LSM ≥10 kPa, FIB-4 >3.25, or APRI ≥1.5 at baseline. The predictors of HCC occurrence and predictive ability of HCC risk scores were assessed.

Results: During a median follow-up of 2.8 years, 28 (1.5%) patients developed HCC at a median of 2.77 years. The mean age was 56 years, and 852 (46.3%) patients were male. When the patients were divided into HCC and non-HCC groups, patients who developed HCC during follow-up were significantly older, and had lower platelet count and albumin level before antiviral treatment. In addition, patients who developed HCC had a higher FIB-4 score (p<0.001). Comorbidities, such as diabetes and hypertension, were more common among patients with HCC than those without HCC (p<0.05). In multivariate analysis, old age, platelet count, albumin level, and sodium level before treatment were significantly associated with the occurrence of HCC (all p<0.05). The high-risk group defined by previously published HCC prediction models showed a significantly high HCC occurrence. This finding was observed in most validated HCC prediction models including aMAP and mPAGE-B, and the incidence of HCC ranged from 1.5% to 7.4% at 3-years and from 3.8% to 24.2% at 5-years at SVR in high-risk patients (Table and Figure). HCC rarely occurred during the first 5-years of follow-up in low and intermediate-risk patients defined by HCC risk scores.

Conclusions: HCC risk models effectively assess the risk of HCC in chronic hepatitis C patients without advanced fibrosis after achieving SVR. Therefore, even in patients without advanced liver fibrosis before treatment, surveillance should be considered if they are included in the high-risk group of the HCC prediction model.

Keywords: Hepatitis C virus, Hepatocellular carcinoma, Risk score

PE-78

An Artificial Intelligence Model for Prediction of Hepatocellular Carcinoma Development after Oral Antiviral Therapy in Patients with Chronic Hepatitis C

Yu Rim Lee[1], Hyun Young Woo[2], Jung Gil Park[3], Min Kyu Kang[3], Jeong Eun Song[4], Byoung Kuk Jang[5], Young Oh Kweon[1], Won Young Tak[1], Se Young Jang[1], Changhyeong Lee[4], Byung Seok Kim[4], Jae Seok Hwang[5], Woo Jin Chung[5], Jeong Ill Suh[6], Jeong Heo[2], Nae-Yun Heo[7], Seung Ha Park[7], Jun Sik Yoon[8], Joonho Jeong[9], Sang Gyu Kwak[10], Yang Hyun Baek[11], Soo Young Park[1]

[1]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea; [2]Department of Internal Medicine, College of Medicine, Pusan National University and Medical Research Institute, Pusan National University Hospital, Busan, South Korea; [3]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, South Korea; [4]Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, South Korea; [5]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea; [6]Department of Internal Medicine, Dongguk University Gyeongju Hos-

pital, Dongguk University College of Medicine, Gyeongju, South Korea; [7]Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, South Korea; [8]Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea; [9]Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, South Korea; [10]Department of Medical Statistics, Daegu Catholic University School of Medicine, Daegu, South Korea; [11]Department of Internal Medicine, Dong-A University Hospital, Busan, South Korea

Aims: Hepatocellular carcinoma (HCC) can still occur after achieving a sustained virologic response (SVR) to direct-acting antiviral (DAA) therapy in patients with hepatitis C. Several models have been developed to predict risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C. We aimed to develop an artificial intelligence-assisted prediction model of HCC risk.

Methods: A total of 3,489 HCV patients who treated with DAAs and had achieved SVR from ten hospitals in South Korea were included in this study. HCC risk prediction models were developed using machine learning including Decision tree and Gradient Boosting.

Results: Age, platelet, AST, ALT, bilirubin, and albumin at baseline and 1 year after treatment were determined to be important factors predicting HCC risk. Prediction models using these parameters at baseline and 1 year after treatment was showed good predictive abilities (AUROC values of 0.83 to 0.86). This model showed significantly better discrimination than previous models.

Conclusions: HCC risk prediction models using machine learning including Decision tree and Gradient Boosting accurately predicted the risk of HCC in patients with chronic hepatitis C who have achieved SVR with DAAs.

Keywords: Chronic hepatitis C, Hepatocellular carcinoma, Deep neural networking

PE-79

Screening, Confirmation, and Treatment Rate of Hepatitis C Virus Infection in Patients Undergoing Surgery in a Single Tertiary Academic Center

Jae Seung Lee[1-3], Hye Won Lee[1-3], Beom Kyung Kim[1-3], Jun Yong Park[1-3], Do Young Kim[1-3], Sang Hoon Ahn[1-3], Seung Up Kim[1-3*]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea, [2]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea, [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: A lack of awareness compromises appropriate consideration of hepatitis C virus (HCV) infections in patients undergoing surgery. We evaluated the status of HCV screening, confirmation, and treatment in patients undergoing surgery.

Methods: Patients who underwent surgery in a tertiary academic center between 2019 and 2021 were eligible for this retrospective study. The testing and positivity rates for anti-HCV antibodies and HCV RNA were analyzed.

Results: Among 96,894 patients (40,121 males, 41.4%) who underwent surgery under general anesthesia, 83,920 (86.6%) were tested for anti-HCV antibodies before surgery. Of these patients, 576 (0.7%) were positive for anti-HCV antibodies and had significantly higher rates of diabetes mellitus (32.6% vs. 18.5%), hypertension (50.5% vs. 28.6%), liver cirrhosis (13.2% vs. 1.7%), and unfavorable laboratory test results compared with those who were negative (all $p<0.05$). The HCV RNA status was assessed in 215 (37.3%) of the anti-HCV antibody-positive patients, and the rate of HCV RNA positivity was 20.5% (n=44 of 215). Of these 44 patients, 42 (95.5%) were referred for treatment, and all 29 treatable patients were successfully treated with direct-acting antiviral therapy. The HCV RNA positivity rate was significantly higher in the hepatobiliary and transplant surgery department (76.6%) than in other surgical departments (25.0–33.5%).

Conclusions: Many preoperative anti-HCV antibody-positive patients did not receive appropriate HCV management. An automated alert system may be required.

Keywords: Hepatitis C virus, Care cascade

PE-80

Rotary International and FIRE Projects

Munkhjargal Ayurzana[1], Munkhnasan Myagmarjav[2], Meredith Potts[3]

[1]Rotary Club of Ulaanbaatar, [2]Flagstaff International Relief Effort, [3]Rotary Club of Flagstaff

Background: In 2017, the Government of Mongolia launched the Healthy Liver Program (HLP) to control viral hepatitis. The collaborative project, Hepatitis Free Mongolia, Phase 2 set the goal of eliminating hepatitis C (HCV) across Sukhbaatar province in rural Mongolia while creating a scalable project.

Methods: To accomplish the elimination of HCV, a few aspects were added to the previous mobile screening model which provides testing for HBV, HCV, ultrasound, fibroscan, examination by specialists and referral to further specialized care and service. These include:
These include:

- The project adopted the best practice initiated by Saga University of Japan to train Hepatitis coordinators to assist every community member to be tested and treated for liver disease.
- A database was created at www.hepatitisfreemongolia.com to record and track testing and treatment results.
- Mobile team consists of Mongolian and Japanese specialists who provide examinations and follow up patient monitoring.
- The project aimed to fill the gaps of HLP and provided financial support for those residents who are unable to afford the treatment.

Results: 80% of the target population has been tested for hepatitis B, C and liver cancer. Out of these people, 12.3% chronically infected with HBV and 5.2% exposed to HCV. Those who were diagnosed with chronic viral hepatitis B, C and suspected with HCC have been referred to the specialized care and treatment.

Conclusions: The successful model created by Hepatitis Free Mongolia, proves elimination of HCV can be accomplished at the provincial level. To achieve the global goal of viral hepatitis elimination by 2030, it contributed to the WHO's framework and criteria for validation of hepatitis elimination. We hope to expand the model across Mongolia and other countries.

[Hepatitis D: Clinical Aspects: Non-Therapy]

PE-81

Relationship of HDV Infection to Increased Risk of Cirrhosis and HCC in Chronic Hepatitis B Patients

Derizal[1], Roland Helmizar[2], Siska Azizah[3]

[1]Department of Tourism, Trisakti Institute of Tourism, Indonesia, [2]Department of Internal Medicine, Baiturrahmah University, Indonesia, [3]Department of Health, Baiturrahmah University, Indonesia

Aims: Chronic hepatitis B patients are at a high risk of developing severe complications, including hepatocellular carcinoma (HCC), which can be fatal. Hepatitis Delta Virus (HDV) is a single-stranded RNA virus that relies on HBV for its propagation. In several countries, a study aims to investigate the correlation between HDV infection and the increased risk of cirrhosis and HCC in patients with chronic hepatitis B.

Methods: This is a systematic literature review with the keywords "HDV Infection", "Cirrhosis", "HCC" and Chronic Hepatitis B Patients with a descriptive analysis research model.

Results: Study by Jang et al. (2021) showed that liver cirrhosis (HR/95% CI 9.98/5.11–19.46, $p<0.001$) was responsible for HCC, and among patients with cirrhosis, HDV RNA positivity was associated with HCC (HR/95% CI 9.98/5.11–19.46, $p<0.001$). In a study conducted by Romeo et al. (2009), they examined 299 patients infected with HDV over 28 years and found that HDV infection persistently led to cirrhosis and HCC at annual rates of 4% and 2.8%, respectively. Oyonsuren et al. (2006) conducted a retrospective investigation of 292 patients with chronic hepatitis and found that HDV coinfection was more strongly associated with HCC at a younger age compared to HCV monoinfection. Another study by Ji et al. (2012) revealed that out of 9,160 HBV patients, 650 had HDV co-infection over a period of 11 years, and HDV was identified as a strong risk factor for an increased risk of HCC.

Conclusions: The presence of HDV infection in chronic hepatitis B patients is strongly associated with an increased risk of developing cirrhosis and hepatocellular carcinoma (HCC), emphasizing the need for management and control of HDV infection to reduce the occurrence of these complications.

Keywords: HDV infection, Cirrhosis, HCC, Chronic hepatitis B patients

[Hepatitis D: Current and New Therapies]

PE-82

Efficacy of Pegylated Interferon-Alpha-2a in Chronic Hepatitis D Infected Patients

Derizal[1], Roland Helmizar[2], Siska Azizah

[1]Departement of Tourism, Trisakti Institue of Tourism, Indonesia, [2]Departement of Internal Medicine, Baiturrahmah University, Indonesia, [3]Departement of Health, Baiturrahmah University, Indonesia

Aims: Hepatitis Delta Virus (HDV) is a distinctive virus that relies on Hepatitis B Virus (HBV) for its replication and survival. The only available treatment option for HDV is Pegylated Interferon-Alpha-2a (PEG-alfa-2a). The objective of this study was to evaluate the effectiveness of PEG-alfa-2a in chronic HDV-infected patients.

Methods: A systematic search through Pubmed/MEDLINE, Scopus, Cochrane Library, and EBSCO was conducted to find this topic. The studies were selected and critically appraised. Data were then analyzed and summarized descriptively.

Results: Study by Nazish Butt et al. included 165 patients were positive for both Anti-HDV and HBsAg, who were treated for 48 weeks with PEG-alfa-2a. Out of the total number of patients, 25 (23%) patients achieved the End Treatment Response (ETR) at the 48-week mark, 27 patients (25%) showed partial response, while 54 patients (50%) experienced treatment failure. Another study by Bazinet M et al was conducted to assess the safety and efficacy of REP 2139 (a drug that clears circulating hepatitis B virus surface antigen) and pegylated interferon alfa-2a in 12 patients with chronic HBV and HDV co-infection. Six patients achieved HBsAg levels less than 50 IU/mL by the end of treatment, and five of them maintained this level of suppression at the end of 1-year follow-up. Additionally, six patients had hepatitis B surface antibody (anti-HBs) titers above 10 mIU/mL at the end of treatment, which were maintained at the end of 1-year follow-up in five patients.

Conclusions: Interferon therapy in patients with CHD shows a sub-optimal outcome. It's important to note that the trial had limitations, such as its non-randomized design and small sample size, which could affect the generalizability of the results. Therefore, further studies, including randomized controlled trials, are needed to establish the efficacy of pegylated interferon-alpha-2a in chronic HDV-infected patients.

Keywords: Pegylated interferon-alpha-2a (PEG-alfa-2a), Interferon, Chronic hepatitis D, Efficacy

[Liver Cancer: Basic and Translational Research]

PE-83

Genetic Analysis of Three Dimensional Structure Like Human Liver, Evaluation Method of Hepatotoxicity and Conjugate Like Human Liver

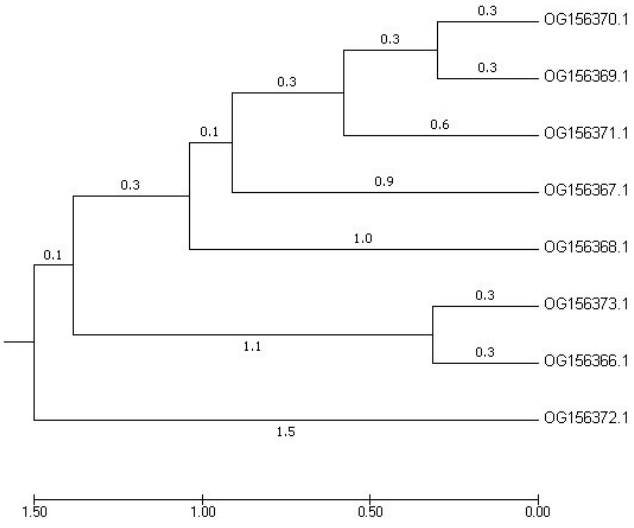
Ramlah[1], Haerani[2]

[1]Department of Biology Education, Universitas Sulawesi Barat, Indonesia, [2]Department of Midwifery, Sekolah Tinggi Ilmu Kesehatan Bina Bangsa Majene, Indonesia

Aims: Genetic analysis is an important force in evolution as it allows natural selection to increase or decrease frequency of alleles already in the population. Genetic disease is mostly caused by familiarity in the genetic code. DNA arrays capable of simultaneously measuring expression of thousands of genes in clinical specimens from affected and normal individuals have the potential to provide information about superior characteristics gene from organism. Genes can be used as markers for cell recruitment and activation molecules. This study

aims to evaluate the genetic analysis of three dimensional structure like human liver, evaluation method of hepatotoxicity and conjugate like human liver.

Methods: Data obtained from 8 nucleotide sequences of three dimensional structure like human liver, evaluation method of hepatotoxicity and conjugate like human liver sequence on secondary data form on https://www.ncbi.nlm.nih.gov/ and selected articles journal evaluated by searching in PubMed, EMBASE, and the Cochrane Library database that have been carried out in the last 5 years (2018-2022). The phylogeny analysis of variations and relationships of DNA sequences was inferred using the UPGMA method and the evolutionary distances were computed using the Maximum Composite Likelihood method using MEGA11 software.



Results: Based on the analysis of variations and relationships, it is known that on the dendogram, 8 sequences were divided into 2 main groups, namely groups A consisting of 7 specimens and groups B consisting of 1 specimens. The optimal tree with the sum of branch length=7.53041418 is shown. The tree is drawn to scale, with branch lengths (next to the branches) in the same units as those of the evolutionary distances used to infer the phylogenetic tree. This grouping is based on the existence of a similar genetic makeup equation with a high bootstrap value indicating the degree of kinship between specimens and the strength of the philogenous trees. Specimens that are in the same sub-groups show a degree of close kinship. On the other hand, specimens from different sub-groupss display distant kinship. Grouping was achieved on the basis of differences in expression levels across individual specimens.

Conclusions: It can be concluded that the variation and relationship of three dimensional structure like human liver, evaluation method of hepatotoxicity and conjugate like human liver sequence have highly variation. Information about kinship can be used as an informative source to assembly of superior genes in living of human cells.

Keywords: Genetic analysis, Three dimensional structure, Human liver

PE-84

Antitumor Effects of Regorafenib on Hepatocellular Carcinoma and MicroRNA Expression

Kei Takuma, Mai Nakahara, Kyoko Oura, Tomoko Tadokoro, Koji Fujita, Joji Tani, Asahiro Morishita, Tsutomu Masaki

Department of Gastroenterology and Neurology, Faculty of Medicine, Graduate School of Medicine, Kagawa University, Japan

Aims: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is one of the leading causes of cancer-related deaths worldwide. Regorafenib, a multi-kinase inhibitor, is used as a second-line treatment for advanced HCC. Here, we aimed to investigate the mechanism of the antitumor effect of regorafenib on HCC and evaluate altered microRNA (miRNA) expression.

Methods: Cell proliferation was examined in six HCC cell lines (HuH-7, HepG2, HLF, PLC/PRF/5, Hep3B, and Li-7) using the Cell Counting Kit-8 assay. Xenografted mouse models were used to assess the effects of regorafenib *in vivo*. Cell cycle analysis, western blotting analysis, and miRNA expression analysis were performed to identify the antitumor inhibitory potential of regorafenib on HCC cells.

Results: Regorafenib suppressed proliferation in HuH-7 cell and induced G0/G1 cell cycle arrest and cyclin D1 downregulation in regorafenib-sensitive cells. We used a custom microarray platform to analyze the expression levels of 2555 miRNA probes. Unsupervised hierarchical clustering analysis showed that the regorafenib group was clustered separately from the control group. Among the miRNAs differentially expressed on regorafenib treatment, miR-3714 is tumor suppressors associated with the decreased expression of cyclin D1. Quantification of miR-3714 by RT-qPCR showed significantly increased expression in the regorafenib-treated group compared to the untreated group. To elucidate the role of miR-3714, we transfected HuH-7 cells with an miR-3714 mimic. Western blotting results confirmed that cells treated with the miR-3714 mimic exhibited a decrease in cyclin D1 expression, similar to that observed in cells treated with regorafenib.

Conclusions: Our study revealed that regorafenib suppresses HCC cell proliferation and HCC tumor growth, and it exerts antitumor effects by inducing cell cycle arrest in regorafenib-sensitive HCC cells. Regorafenib suppresses cell proliferation and tumor growth in HCC by decreasing cyclin D1 via alterations in intracellular and exosomal miRNAs in HCC.

Keywords: Hepatocellular carcinoma, Regorafenib, Micro RNA, Cyclin D1

PE-85

Evaluation of Alpha-Fetoprotein (AFP) Test in the Diagnosis of Hepatocellular Carcinoma

Le Hien[1], Le Quoc Tuan[2]

[1]Thai Nguyen University of Medicine and Pharmacy, [2]103 Cam Khe Clinic, Vietnam

Aims: Background: Hepatocellular carcinoma (HCC) remains one of the most invasive cancers in humans, mostly occurring in patients

with chronic liver disease, and the third leading cause of cancer-related death throughout the world. Alpha-fetoprotein (AFP) is the only tumor biomarker routinely used for the treatment of HCC. AFP is strongly correlated to tumor aggressiveness. Its levels are related with poorly differentiated HCC, tumor size and microvascular invasion.

Aims: To evaluate the AFP test in the diagnosis of HCC.

Methods: A prospective cross-sectional descriptive study of HCC patients examined and treated at 103 Cam Khe Clinic from January 2020 to December 2022. Combined estimates for sensitivity and specificity were statistically analyzed by random-effects model using MetaDisc 1.4 and Stata 15.0 software at the prespecified threshold of 400 ng/mL. The optimal threshold was evaluated by the area under curve (AUC) of the summary receiver operating characteristic (SROC).

Results: With AFP threshold of 400 ng/mL showed the summary sensitivity and specificity of 0.33 (95% CI 0.30–0.35) and 0.95 (95% CI 0.94–0.98), respectively. AFP level and the combined scores of GALAD (Gender Age Leuthin Alphafetoprotein Decarboxyl), GALADUS (Gender Age Leuthin Alphafetoprotein Decarboxyl Ultrasonography) have low degree of correlation with tumor size in the HCC group. AFP level has low correlation with WBC and PLT. The GALAD, GALADUS scores are positively correlated with AFP, AST, WBC, PLT. GALADUS score has low level of positive correlation with ALT.

Conclusions: Combining the AFP marker and using GALAD, GALADUS scores will give high sensitivity and specificity in the diagnosis of HCC.

Keywords: Alpha-fetoprotein (AFP), Diagnosis, GALADUS (gender age leuthin alphafetoprotein decarboxyl ultrasonography), Hepatocellular carcinoma, GALAD (gender age leuthin alphafetoprotein decarboxyl)

PE-86

Hesperidin Attenuates DEN Induced Liver Cancer in Rats via Inhibition of Activation of AMPK and Blocking of mTOR-Dependent Signaling Pathway

Deepika Singh

SHUATS, India

Aims: The excessive buildup of the extracellular matrix that characterizes liver fibrosis is a wound-healing response to chronic liver diseases/ inflammatory diseases and also lead to liver cancer When liver cancer and mammalian target of rapamycin (mTOR) activity are present, inhibition of AMPK activity may be a key mechanism. In the current work, we examined the impacts of hesperidin against DEN-induced liver cancer in rats and its underlying mechanism.

Methods: An intraperitoneal injection of the DEN was injected into the ratat a dose level of 100 mg/kg per week for five continuous weeks. All the rats were randomly divided into 5 groups and treated with hesperidin for 5 weeks. The serum and liver tissue from all group rats were used for the estimation of biochemical parameters (hepatic, non-hepatic parameters, antioxidant parameters, and proinflammatory cytokines). We also evaluated the gene expression study. A histopathological study was performed to examine the effect of the drug on the liver.

Results: Hesperidin significantly elevated the level of aspartate transaminase, alkaline phosphatase acid phosphatase, blood urea nitrogen, creatinine, and total protein. It also significantly ($p<0.05$) suppressed the antioxidant profile malondialdehyde (MDA,) glutathione-S-transferase (GST), catalase, and superoxide dismutase. It also significantly ($p<0.05$) reduced the sα-SMA, TIMP-1, and collagen I protein expressions It also inhibited the phosphorylation of PI3 K and Akt, enhanced the p-AMPK expression, and reduced p-mTOR.

Conclusions: The result of the present study indicates that hesperidin induced the HSC activation apoptosis and attenuated liver cancer via inhibition of mTOR and AMPK activation signaling pathways.

Keywords: Liver cancer, Hesperidin, Signaling pathway

PE-87

Biofabrication and Characterization of Cationic Lipid Nanoparticles of Quercetin against DEN-Induced Liver Cancer in Rats

Niti Singh, Deepika Singh

Marlabs Innovation Pvt.LTD, SHUATS, India

Aims: HCC is the most common type of solid tumor and is brought on by the persistence of hepatitis B, C, or any other liver infection, which causes persistent inflammation in the liver.The creation and assessment of quercetin-loaded cationic solid lipid nanoparticles (QCSLNs) for the treatment of hepatocellular carcinoma (HCC) are the main objectives of the current work.

Methods: Utilising a factorial design, the formulation was optimized, and further *in vitro* drug release, cytotoxicity, biodistribution, *in vivo* preclinical testing, and biochemical evaluations were conducted.

Results: The improved formulation demonstrated stability over a 12-week storage period at 25°C/60% RH, homogeneous disparity, uniform size, and positive zeta potential. The *in vitro* drug release and cytotoxicity investigation found that quercetin-loaded cationic solid lipid nanoparticles (QCSLNs) was more hazardous to HepG2 cells than QC solution, with a 60% drug release rate in the first six hours. Additionally, a study on the biodistribution and anticancer effect of QCSLNs in a rat model of HCC revealed a larger accumulation of QCSLNs in the tumour tissue than QC solution and QCSLNs (P0.01). Additionally, QCSLNs demonstrated a strong balance between antioxidant enzymes and pro-inflammatory cytokine levels. Histopathological analysis revealed a decrease in the number of hepatic nodules, necrosis formation, inflammatory cell infiltration, inflammatory blood vessel changes, and cell swelling.

Conclusions: Overall, the findings suggested that increased anticancer activity in QCSLNs was clearly demonstrated by *in vitro*, *in vivo*, and biochemical tests.

Keywords: Lipid nanoparticals, Quercetin, DEN

PE-88

In Vitro and in Vivo Antitumor Effect of Biofabricated Silver Nanoparticles of Caffeic Acid against Hepatocarcinogenesis by Upregulation of Bax/Bcl2

Ekta Yadav

Sam Higginbottom University of Agriculture Technology and Sciences, India

Aims: Over recent years, metal nanoparticles, especially silver (Ag) nanoparticles have been accepted as promising therapeutic tools for cancer diagnosis as well as treatment. Caffeic acid (CFA) is a natural phenolic acid that possesses antitumor activity. The current study was designed to explore the *in vitro* and *in vivo* antitumor effect of CFA-mediated biofabricated silver nanoparticles (CFA-AgNPs) against hepatocellular carcinoma (HCC).

Methods: CFA-AgNPs were synthesized by co-precipitation method and characterized by various techniques such as ultraviolet-visible spectroscopy, fourier-transform infrared spectroscopy (FTIR), energy dispersive X-ray analysis (EDX) and field emission scanning electron microscopy (FESEM). Cytotoxic potential of CFA-AgNPs was investigated by MTT assay on HepG2 cells by *in vitro* method. Subsequently, apoptosis and associated gene expression were determined by using flow cytometry assay and quantitative real-time polymerase chain reaction (qPCR), respectively. *In vivo* study was performed in male Sprague Dawley rats by inducing diethylnitrosamine (DEN, 200mg/kg) administration and the CFA-AgNPs were given by oral gavages at two different dose levels (10 and 20mg/kg for 16 weeks). On the last day of the study, various antiproliferative parameters were determined including hematological profile, serum biomarkers and inflammatory cytokine levels for each group.

Results: Characterization techniques confirmed the formation of spherical crystalline CFA-AgNPs with a size range of 50-80 nm and having a strong peak of Ag. FTIR results showed the existence of possible bioactive functional groups of phytoconstituents in the synthesized CFA-AgNPs. Further, CFA-AgNPs exhibited significant (p<0.05) cytotoxic effects and flow cytometry results revealed stimulation of apoptosis. An increase in p53 and Bax expressions and a reduction in Bcl-2 expression along with upregulation of accompanied Bax/Bcl-2 ratio were observed in qPCR results. *In vivo* results demonstrated that the CFA-AgNPs administered group significantly downregulated (p<0.01) the serum marker hepatic and non-hepatic enzymes and proinflammatory markers such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) as compared to DEN alone group.

Conclusions: Results of the current investigation recommended the inhibition potential of CFA-AgNPs against DEN-induced damaging effects on the liver via an antioxidant defense system and modulation of Bax/Bcl2 as well as proinflammatory cytokines. CFA-AgNPs can be utilized as a superior approach to improve the clinical results against HCC.

Keywords: Hepatocellular carcinoma

PE-89

Chemoprotective Effect of Crocetin-Dextrin Nano-Formulation against N-Diethylnitrosamine Induced Hepatocellular Carcinoma in Wistar Rats via Mitochondrial Apoptosis, Antioxidative, Anti-Inflammatory and PI3K/Akt/mTOR Signaling Pathways

Vikas Kumar[1], Firoz Anwar[2]

[1]Natural Product Drug Discovery Laboratory, Department of Pharmaceutical Sciences, Faculty of Health Sciences, Sam Higginbottom University of Agriculture, technology & Sciences, Prayagraj -211007,Uttar Pradesh, India, [2]Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia, India

Aims: Hepatocellular carcinoma (HCC) is known to have a high prevalence, particularly in regions with a high incidence of chronic liver diseases such as hepatitis B and C infections, alcoholic liver disease, and non-alcoholic fatty liver disease. In this study, we fabricate the crocetin-dextrin nano-formulation (CDNF) against N-diethylnitrosamine (DEN) induced hepatic cancer in rats.

Methods: Crocetin-Dextrin nano-formulation was prepared from the aqueous nanoemulsion of crocetin and dextrin. The Wistar rats were divided into different groups and DEN (200 mg/kg) was used for the induction of HCC in rats and received the oral administration of crocetin and CDNF for 20 weeks. The microscopical study was carried out for the confirmation of hepatic nodules. Liver indices like alpha-fetoprotein (AFP), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), albumin, bilirubin, total protein, C-reactive protein (CRP); oxidant parameters such as superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx), malonaldehyde (MDA) activity along with nitric oxide (NO); inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-10); inflammatory parameters viz., cyclooxygenase-2 (COX-2), prostaglandin (PGE2), vascular endothelial growth factor (VEGF) and Inducible nitric oxide synthase (iNOS) levels were estimated. The level of AKT, mTOR, Bax, p-53, Bcl-2, caspase-3 and PI3K gene were estimated.

Results: CDNF treatment remarkably reduced the tumor size, average size of nodules and tumor nodules. CDNF also reduced the body weight and suppressed the levels of AFP, AST, ALT, ALP, albumin, bilirubin, total protein and CRP. CDNF also altered the levels of antioxidant parameters like MDA, GPx, GSH, CAT and NO. CDNF significantly (p<0.001) reduced the levels of TNF-α, IL-1β, IL-6 and improved the level of IL-10. CDNF also suppressed the levels of inflammatory parameters viz., COX-2, PGE2, VEGF and iNOS, respectively. CDNF also altered the level of gene expression like AKT, mTOR, Bax, p-53, Bcl-2, caspase-3 and PI3K. Histopathologicalobservationsn suggest that CDNF treated rats exhibited fewer necrotic and inflammatory cells.

Conclusions: The result suggests that CDNF was able to alter the HCC in the rats via regulation of Bax/Bcl-2/p53 and PI3K/Akt/mTOR signaling pathways.

Keywords: Crocetin-dextrin nano-formulation, Hepatocellular carcinoma, Inflammation, Apoptosis

PE-90

1H-NMR-Based Metabolomics Testing for Hepatocellular Carcinoma Potential of Umbelliferone on Diethyl Nitrosamine (DEN) Induced Metabolic Alteration

P Bhatt[1], A Sahoo[2], D Kumar Patel[2], V Kumar[2]

[1]Department of Biotechnology, Fermentis Biotech, India, [2]Department of Pharmacy, SIHAS, India

Aims: Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, having highest prevalence in the developing countries and it's showing sustained growth across the developed world. NMR based metabolomics proffer a complementary approach that provides the information on the functional integrity of whole organism over time after the drug treatment. In the current study, we attempted to scrutinize the ^{1}H-NMR based metabolic profile investigation to implemented on rat serum to explore the effect of Umbelliferone (UF) on diethyl nitrosamine (DEN) induced HCC.

Methods: Intraperitoneal administration of DEN was used to induce the HCC in Wistar rats. The rats were divided into different groups and orally treated with UF till 22 weeks. The anticancer effect of UF was assessed in term of estimation of various biochemical parameters and hepatic histopathology analysis. Plasma of all group rats were collected upon the sacrifice and NMR based serum metabolic investigation was implemented to scrutinize the effect of UF on metabolic alterations.

Results: UF demonstrated the protective effect on the hepatic tissue and altered the hepatic cells into the normal proportion. HPLC showed the excellent plasma drug concentration after the UF administration. During the HCC, citric acid, bile acids, energy metabolism, purine metabolism and several amino acids metabolism were significantly altered in DEN group and UF treatment showed the modulation of these acids metabolism during the hepatic disease. The score plots of NMR suggest that UF ameliorated the HCC induced metabolic alterations which suggest the anticancer effect of UF.

Conclusions: The result of the study suggests that UF may suppress the increased energy metabolism of HCC cells. The cancer selective metabolic pathways identified in the current experimental study will be key targets of the anticancer activity of UF.

Keywords: Metabolomics, Hepatic cancer, Umbelliferone, Inflammation

PE-91

Solid Lipid Nanoparticle of Alpha-Mangostin Exerts Diethylnitrosamine Induced Hepatocellular Carcinoma via Alteration of PI3K/Akt Pathway

D Chauhan[1], V Kumar[2], D Kumar Patel[3]

[1]Department of Applied Physics, RK College of Sciences, India, [2]SHUATS, India, [3]Chandra Shekhar Singh College of Pharmacy, India

Aims: Hepatocellular carcinoma (HCC) is the widely documented danger to the liver and 3rd most common reason for tumor death around the world. Identification of oncogene and its related possible pathway is crucial for understanding therapy resistance and effectual treatment. Researcher targeted the 5-bisphosphate 3-kinase/protein kinase B, phosphatidylinositol-4 and mitogen activated protein kinase's pathway to suppress the cell proliferation and expansion. We made attempt to fabrication the solid lipid nanoparticle (SLN) of alpha-mangostin and examine against the diethylnitrosamine (DEN) induced HCC and explore possible mechanism of action.

Methods: Double emulsion solvent displacement model was used for the preparation of alpha-mangostin-SLN. Intraperitoneal injection of DEN (200 mg/kg) was used for induction the HCC and various parameters were scrutinized. The genetic effects HP-SLN on Pdk1, Akt1, Pik3r1, Map3k1, Erbb2, PIk3ca using semi-quantitative RT-PCR analysis were assessed. Morphological and histopathological component of hepatic tissue were estimated.

Results: Surface methodology suggests the 182.3 nm particle size and 0.230 polydispersity index for alpha-mangostin-SLN. alpha-mangostin-SLN significantly (p<0.001) reduced the hepatic nodules (84.5%) and hepatic nodules (93.4%). alpha-mangostin-SLN significantly (p<0.001) modulated the hepatic parameter viz., AFP (83.4%), CEA (50.4%), ALT (58.5%), ALP (68.4%), AST (65.8%), GGT (63.4%); non-hepatic parameter viz., BUN (56.4%), total protein (64.5%), albumin (63.4%), direct bilirubin (67.4%), bilirubin (63.4%); antioxidant parameter LPO (71.3%), SOD (60.3%), CAT (64.9%), GPx (58.3%), GST (63.4%) respectively. alpha-mangostin-SLN significantly (p<0.001) modulated the expression of Pik3r1(58.4%), Akt1(43.5%), PIk3ca (54.9%), Erbb2 (53.6%) and Map3k1 (43.6%). Morphological and histopathological studies advice and support the above result by alpha-mangostin-SLN.

Conclusions: Collectively, we can conclude that alpha-mangostin-SLN regulated the PI3K and Akt pathways, which involved in reduction of heatic cancer expansion and proliferation and its chemo-protective effect.

Keywords: Liver Cancer, Alpha mangostin, PI3K/Akt pathway, Inflammation

PE-92

Staging of Ovarian Cancer on the Basis of Liver Metastasis

Amar Ranjan, Harshita Dubey, Shuvrojyoti Mondal, Kartikeya

All India Institute of Medical Sciences, New Delhi, India

Aims: Metastasis lesions in the liver follow a unique pattern in peritoneal malignancies including ovarian cancer (OC). In (OC), if the tumor spreads to the liver from the peritoneum, it is categorized as FIGO stage III, but if there is hematogenous spread to the liver, it is categorized as stage IV of ovarian cancer. Here we discuss a unique case of OC with liver nodules.

Methods: Case study

Results: A 37-year-old female presented with loss of appetite, abdominal distension & supraumbilical swelling. CA 125 was 1888.5 IU/L. MRI showed bulky ovaries, ascites, retroperitoneal lymphadenopathy, omental & supraumbilical nodules with herniation, nodules on the liver surface, and moderate pleural effusion in the right chest. Ascitic fluid Cytology showed malignant cells. US-guided FNAC from

omental nodule confirmed Adenocarcinoma. Considering Ovarian Carcinoma stage 3C, 3# TP regimen was given as neoadjuvant chemotherapy (CT). After 1# CT, alopecia was seen. Then suboptimal cytoreductive surgery was done, which was followed by 3 cycles of TP regimen. Treatment-free interval was seen for 4 months. On follow-up; Clinical, radiological & serological investigations showed progressive disease. Oral metronomic therapy with oral CE (cyclophosphamide and etoposide for 1-5 days, every 21 days) was given. After 2 cycles the response was poor with PS-2 & CA 125 3830 IU/L. CECT showed progressive disease. Gemcita + cisplatin (GC) regimen was started with D1, D15 plans. This was being tolerated well. Post CT#2; GR 2 thrombocytopenia was seen. POST 3# GC regimen no response was seen. Now weekly Paclitaxel was given. As a last option, in case of no response after 2, the BSC regimen (Paclitaxel + Carboplatin +Bevacizumab) remains an option.

Conclusions: This case was categorized as FIGO stage IV A. Liver surface involvement was considered as peritoneal spread. Pre and post debulking surgery chemotherapy with TP regimen is the standard protocol for management.

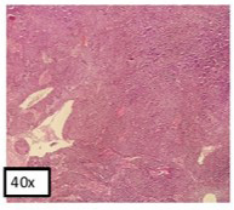


Figure 1: HGSC of ovary, 40x, H & E stain

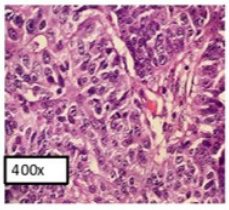


Figure 2: HGSC of ovary, 400x, H & E stain

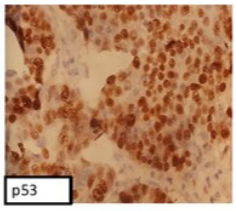


Figure 3: IHC of ovary, 400x, P53 stain

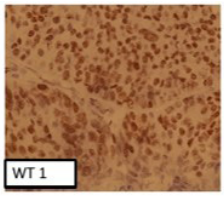


Figure 4: IHC of ovary, 400x, wt1stain

Keywords: Liver metastasis, Ovarian cancer, Debulking surgery

PE-93

Exosomal miRNA-720 Contributes to Hepatocellular Carcinoma Progression by Regulating StarD13

Ji Min Kim[2,3], Hye Seon Kim[2,3], Jin Seoub Kim[2,3], Ji Won Han[1,2], Soon Kyu Lee[1,2], Heechul Nam[1,2], Pil Soo Sung[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2*]

[1]Department of Internal Medicine; [2]The Catholic University Liver Research Center; [3]Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Circulating exosomal microRNAs (miRNAs) have the potential to act as diagnostic and prognostic biomarkers for cancer. This study aimed to identify specific miRNAs in serum exosomes of patients with hepatocellular carcinoma (HCC) and to validate their biological functions as novel diagnostic and predictive biomarkers.

Methods: Serum exosomal miRNAs in patients with HCC (n=241) and without HCC (n=45) were measured by qRT-PCR. The role of exosomal miRNAs in HCC was investigated through *in vitro* tests and verified in a clinical cohort of patients.

Results: *In vitro*, we observed delivery of exosomal miR-720 to recipient cells. Exosomemediated miR-720 promoted proliferation and inhibited apoptosis of recipient HCC cells. Exosomal miR-720 inhibited tumor suppressor StarD13 expression in recipient cells. In addition, exosomal miR-720 promoted stemness in recipient cells by increasing protein expression of stemness-associated markers such as OCT4 and c-MYC. In our cohort series, serum exosomal miR-720 was significantly upregulated in HCC patients than in non-HCC patients, showing an excellent diagnostic performance for HCC. Particularly, exosomal miR720 exhibited superior performance in diagnosing small HCC (<2 cm) compared with AFP or DCP. Exosomal miR-720 levels were positively correlated with advancing tumor stage and size. Patients with high expression of exosomal miR-720 had significantly shorter time to progression than those with low expression of exosomal miR-720 during transarterial chemoembolization (TACE).

Conclusions: Our results demonstrate that exosomal miR-720 plays an oncogenic role in HCC by targeting StarD13. Circulating exosomal miR-720 could be used as a novel diagnostic and therapeutic biomarker and serve as a guide for selecting treatment options including TACE for HCC.

Keywords: Biomarker, Exosome, Hepatocellular carcinoma, StarD13, miR-720, Stemness

PE-94

Inflammatory Cytokine Multiplex Analysis in Patients with Hepatocellular Carcinoma

Jae Mo Han[2,3], Ji Min Kim[2,3], Hye Seon Kim[2,3], Jin Seoub Kim[2,3], Ji Won Han[1,2], Soon Kyu Lee[1,2], Pil Soo Sung1,2, Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2*]

[1]Department of Internal Medicine; [2]The Catholic University Liver Research Center; [3]Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Previous studies have reported the potential clinical value of certain cytokines involved in tumor progression. The roles of multiple cytokines in the clinical outcomes of hepatocellular carcinoma (HCC) are incompletely understood. The aim of our study is to identify clinically significant cytokines that have the potential for diagnostic or prognostic value for patients with HCC.

Methods: Multiple inflammatory cytokines including interferon (IFN)-γ, interleukin (IL)-10, IL-12, IL-17, IL-10, IL-2, IL-6, and tumor necrosis factor (TNF)-α were measured in 174 patients using multiplex immunoassay. The cytokines levels were analyzed in relation to tumor characterization, disease phenotype, and patient survival.

Results: When analyzed according to tumor stage, IL-6 and IL-10 levels were significantly higher in intermediate-to-advanced stage HCC than in early stage HCC among all patients. TNF-α levels positively correlated with tumor stage progression. IL-10 had a marginal correlation with tumor stage. In addition, lower level of IL-10 was associated with significantly better patient survival. Similar findings were observed in patients with HBV-associated HCC. Together with IL-6

and TNF-α, IL-12 has positive correlation with tumor stage in patients with HBV-associated HCC.

Conclusions: Cytokine profiling provides insights into the involvement of multiple and complex inflammatory features through an early to advanced stage of HCC as well as the potential of these combined cytokine biomarker approaches to predict outcomes in HCC.

Keywords: Hepatocellular carcinoma, Cytokine, Biomarker, Prognosis

PE-95

Depression Level among Elderly with Liver Function Decrease and Hypertension Status

Rosinta Hotmaida Pebrianti Purba

Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia

Aims: Indonesia is entering an aging society with the elderly population reaching 29,3 million (10,8%). In Indonesia, liver disease is the highest comorbid factor in increasing the risk of death by 19.5 times in the elderly age group when the complications make it even worse.

Methods: Using data from the 2014 Indonesia Family Life Survey (IFLS), this study aims to analyze mental health problems in older adults (60+) with liver cancer and Hypertension status. IFLS is representative of 83% of the Indonesian population.

Results: The analysis shows that the Elderly with hypertension reaches 42% (male: 60,7%), Elderly with liver cancer reach 6,1% (male: 70,6%). The elderly with both problems reaches 0,7% dan 55% of them experienced mental health problems and the percentage is higher in women. Based on 10 depression assessment questionnaires, the symptoms are: (1) I was bothered by things that usually don't bother me; (2) had trouble concentrating on what I was doing; and (3) I felt everything I did was an effort. However, the percentage of elderly with liver cancer and hypertension experiencing mental health problems will decrease by 6,78% when they have a cell phone. Nearly half of older people's educational attainment is in elementary school, which reaches 46.05 percent. Generally, the elderly with higher digital literacy prefer to seek treatment at a formal health facility than traditional practitioners such as shamans. They tend to seek outpatient care treatment at a community health center or Puskesmas (44,11%), specialist (29,41%), and private hospital (11,76%).

Conclusions: Increasing digital aging encourages elderly health literacy, as well as decreasing mental health problems. Mainstreaming the digital aging issue can help various information and services needed by the elderly to be healthier, independent, and with dignity.

Keywords: Mental health, Complication, Digital aging, Elderly with liver disease

PE-96

The Management and Protocol of Liver Transplant (LT) in the Era of the COVID-19 Pandemic: Strategy to Minimize Risk of Exposure to Hazards

Ester Marnita Purba[1], Helen Try Juniasti[2], Rosinta H P Purba[3]

[1]Department of Industrial Engineering, Widyamataram University, Yogyakarta, Indonesia, [2]Department of Public Health, Cendrawasih University, Papua, Indonesia, [3]Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia

Aims: Liver transplantation (LT) more than tripled during the COVID-19 pandemic. However, this situation has upended significant disruption in all aspects of healthcare worldwide and led to an inevitable decrease in LT activity. Clinicians difficult decisions to suspend or continue a life-saving procedure based on the scarce available evidence regarding the risk of transmission and mortality in immunosuppressed patients. Therefore, ethical frameworks balance the need for LT.

Methods: Using an electronic database under PRISMA guidelines, this review will provide an updated view of the impact of the pandemic on LT programs worldwide. Ten articles were selected for inclusion regarding donor and recipient screening, strategies for waitlist prioritization, and post-transplant risk of infection and mortality.

Results: The mortality rate increased by 32,7% in LT candidates with COVID-19 because of respiratory failure, increased age, and the presence of comorbidities. Previous symptomatic SARS-CoV-2 infection did not affect early post-transplant survival. The viral infection suggests that management of immunosuppression without mycophenolate mofetil or m-Tor inhibitors may be beneficial. It is also essential to pay attention to possible drug interactions, especially in the case of tacrolimus, with some of the treatments with antiviral effects given in the context of COVID-19 (lopinavir/ritonavir, azithromycin). However, the dismal prognosis of patients with decompensated cirrhosis supports the adoption of strict precautions and urgent testing of the efficacy of vaccination in this population. Strategies to minimize risk exposure to the transplant population and health workers include systematic virus screening, protection devices, social distancing, and reduction of patients visits to the transplant center.

Conclusions: Factors that should be preferentially considered are related to a new strategy on medical care for patients with LT during the COVID-19 pandemic. Those centers where the activity continued or was heavily restricted were obliged to screen donors and recipients, design COVID-safe clinical pathways, and promote telehealth to prevent nosocomial transmission.

Keywords: Liver transplantation, Viral infection, Clinical pathaway, Immunosuppression

PE-97

The Gate Keeper System in Accessing Health Services, Can It Prevent Liver Failure Patients from Out of Pocket?

Lintong Hottua Simbolon[1], Helen Try Juniasti[2], Rosinta H P Purba[3], Ester Marnita Purba[4]

[1]Department of Law, University of Lampung, Lampung, Indonesia, Department of Industrial Engineering, [2]Department of Public Health, Cendrawasih University, Papua, Indonesia, [3]Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia, [4]Widyamataram University, Yogyakarta, Indonesia

Aims: Chronic liver diseases (CLD) and cirrhosis are substantial health burdens worldwide. In Indonesia, the total direct medical cost attributable to liver cancer in 2020 was estimated to be approximately US$3.8 million. According to the latest WHO data published in 2020 Liver Disease Deaths in Indonesia reached 89,583 or 5.30% of total

deaths.

Methods: Using the juridical-empirical approach, this study analyzes whether Indonesia's health service practices' conformity is in line with national policy objectives. In accordance with the National Social Security and Law Number 11 of 2009 concerning Article 19 of the Law concerning Social Welfare, the government is obliged to ensure equal health services access and facilities due to Universal Health Coverage.

Results: JKN aims to protect the citizen from financial risks through the Social Security Organizing Agency (BPJS) which will cover all types of diseases (Minister of Health Regulation 28/2014). Thus, the cost burden allocated by the BPJS for curative liver failure absorbs U$198 million in 2014 and U$297 in 2016. Meanwhile, almost 784.3 thousand individuals each year fall into poverty as a result of liver health costs. In fact, BPJS coverage is not fully cover hypertension treatment such as only 30 days of chronic medicine. The patient has to spend the cost of illness that is borne for life by 2.7 percent of total household consumption expenditure. This has an impact on reducing the quality of life of patients.

Conclusions: The result concludes that the government has not achieved the goal of eliminating liver disease patients from "out of pocket" yet. The government needs to overcome the health policies overlapping and develop hospital formularies due to prevention and health promotion programs.

Keywords: Out of pocket, Integrated care system, Gate-keeper system, Social insurance

PE-98

Genomic Characteristics of Hepatocellular Carcinoma Patients with Response to Sorafenib

Sun Young Yim[1], Jong Su Kim[1], Chang Hee Jung[1], Jung Jun Young[1], Young Sun Lee[2], Seong Hee Kang[3], Tae Hyung Kim[3], Young Kul Jung[3], Ji Hoon Kim[2], Yeon Seok Seo[1], Hyung Joon Yim[3], Jong Eun Yeon[2], Kwan Soo Byun[2], Ju-Seog Lee[4]

[1]Department of Internal Medicine, Korea University Anam Hospital, [2]Department of Internal Medicine, Korea University Guro Hospital, [3]Department of Internal Medicine, Korea University Ansan Hospital, [4]Systems Biology, Md Anderson Cancer Center

Aims: Sorafenib is a multiple receptor tyrosine kinase inhibitor which is the standard systemic therapy for advanced hepatocellular carcinoma (HCC). However, the objective response rate is low only reaching 10% and since there are other new 1st line treatment options such as lenvatinib and immune checkpoint inhibitors, biomarkers that may predict patients who will respond well to sorafenib is required. We implemented RNA sequencing (RNA-seq) in HCC tumors to identify potential biomarkers that would predict response to sorafenib and uncover underlying biological features associated with better response.

Methods: A total of 33 patients who had undergone liver resection prior to sorafenib treatment were enrolled. Matched tumor/surrounding tumor tissues were obtained and RNA-seq was performed with the NextSeq500. Cluster analysis was performed and gene signature associated with sorafenib response was identified. The gene signature was validated in independent Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma (STORM) cohort. Gene network analysis by Ingenuity Pathway Analysis (IPA) was performed to uncover activated pathways and key upstream regulators associated with response to sorafenib. The composition of infiltrated immune cells in tumors was also investigated by using the CIBERSORTx algorithm.

Results: The mean age was 58±11 years with male predominance (81.8%), median child pugh score was 5 (range, 5-8) and 57.6% of the patients switched to second-line chemotherapy mostly due to HCC progression. The best response among 33 patients was complete response (CR) observed in 1 patient, partial response (PR) in two patients, stable disease (SD) in 12 patients while 18 patients showed disease progression. Gene signature (721 genes) associated with disease control (SD, PR, CR vs. no response) was derived using cluster analysis and was named as Korea University Sorafenib Response (KUSOR) gene signature. When applied on STORM cohort, KUSOR gene signature was able to predict patients who do not recur on adjuvant setting of sorafenib treatment after HCC resection or ablation with sensitivity of 91% and specificity of 74%. Gene network analysis by IPA revealed that patients who showed disease control were characterized by IL-6 and IL-1ß activation. In contrast, MYC was more activated in HCC tumors showing no benefit of the treatment, suggesting that MYC may trigger resistance of HCC cells to sorafenib. In addition, regulatory T cells (Treg cells) and M2 macrophage fractions were significantly higher in poor response group while the fraction of activated NK cells and CD4 cells were substantially higher in disease control group.

Conclusions: Our study reveals that KUSOR gene signature was able to identify patients who would show disease control when treated with sorafenib. MYC promotes hepatocarcinogenesis in chronic liver disease and overexpression is associated with poor response. Furthermore, it can also be inferred that poor response to sorafenib could be related immune evasion through overexpression of Treg cells and M2 macrophages in tumor microenvironment. Our study is in accord with previous studies where patients with high MYC activation showed poor response to sorafenib indicating that combination therapy such as immune checkpoint blockade should be recommended for these patients.

Keywords: HCC, Sorafenib, Overall survival, Recurrence

PE-99

Chemoprotective Effect of Crocetin against Hepatocellular Carcinoma via Interaction of Gut Microbiota and Biochemical Mechanism

Vikas Kumar,[1] F Anwar[2]

[1]Department of Pharmaceutical Sciences, Shalom Institute of Health & Allied Sciences, Sam Higginbottom University of Agriculture, Technology & Sciences, Prayagraj, India, [2]Department of Biochemistry, King Abdulaziz University, Saudi Arabia, India

Aims: Crocetin is a plant derived natural apocarotenoid dicarboxylic acid that showed the pharmacological activity against the various diseases. Previous report focused on the colorectal cancer effect, still chemoprotective effect against hepatic cancer still unexplored. In this study, we scrutinized the chemoprotective effect of crocetin against the diethylnitrosamine (DEN) induced hepatocellular carcinoma (HCC) in rats and explore the underling mechanism.

Methods: Single intraperitoneal injection of DEN (200 mg/kg) was used for the induction of HCC in rats. The rats were divided into different groups and received the oral administration of crocetin till 22 weeks. The rats hepatic nodules were macroscopically and microscopically evaluated. The hepatic, antioxidant, non-hepatic, inflammatory parameters and cytokines were estimated. The faecal microbiota was used to investigate the chemoprotective effect of intestinal microbiota.

Results: Crocetin effectively suppressed the incidence of tumor nodules, incidence and weight of hepatic tissue. Crocetin significantly (p<0.001) suppressed the hepatic parameters like alpha feto protein (AFP), aspartate transaminase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), acid phosphatase (ACP); non-hepatic parameters viz., total protein, blood urea nitrogen, creatinine; antioxidant parameters include catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), glutathione-S-transferase (GST), superoxide dismutase (SOD), malondialdehyde (MDA) and protein carbonyl. Crocetin considerably suppressed the level of inflammatory cytokines and inflammatory mediators. Crocetin also altered the relative abundance of *Bacteroides, Mucispirillum, Brevundimonas, Lactobacillus, Clostridium* and *Alloprevotella*.

Conclusions: We can say that crocetin remarkably exhibited the chemoprotective effect against the DEN induced HCC in rats via alteration of oxidative stress, inflammation and gut microbiota.

Keywords: Crocetin, Hepatic cancer, Inflammation, Gut microbiota

PE-100

Differential Expression of Telomerase Reverse Transcriptase and Cytokines in Male and Female Patients with Hepatocellular Carcinoma

Jin Seoub Kim[2], Hye Seon Kim[2], Ji Min Kim[2], Jung Hyun Kwon[1], Ji Won Han[1], Pil Soo Sung[1], Si Hyun Bae[1], Jong Young Choi[1], Seung Kew Yoon[1], Jeong Won Jang[1]*

[1]Department of Internal Medicine College of Medicine, The Catholic University of Korea, [2]The Catholic University Liver Research Center Department of Biomedicine & Health Sciences, Graduate School, College of Medicine, The Catholic University of Korea

Aims: Telomerase reverse transcriptase (TERT) abnormalities are the most common altered pathway in hepatocellular carcinoma (HCC), an inflammation-induced cancer. HCC is characterized by male predominance in incidence, with an estimated male-to-female ratio of 3-4:1. Little is known regarding the role of TERT abnormalities and inflammatory cytokines in hepatocarcinogenesis. This study aimed to investigate the association of the TERT gene and cytokines with gender disparity in HCC.

Methods: The study included a total of 357 patients with stored liver tissues or serum. TERT expression was measured in tumor tissues by quantitative real-time PCR, and multiple cytokines were detected in patients' serum by multiplex immunoassay.

Results: Overall, TERT expression was higher in HCC than in Non-HCC tissues (p=0.0001). Among HCC patients, males had higher TERT expression than females (p=0.0001). The levels of cytokines, such as INF-γ, IL-10, IL-12, IL-17, IL-2, IL-6, and TNF-α were not different between male and female patients. When analyzed within patients with HBV-associated HCC, males had higher levels of both IL-6 and TERT expression than females. Among the cytokines, only IL-6 positively correlated with TERT expression in male patients, but not in female patients. The correlation between serum IL-6 and tumor TERT levels appeared to be stronger in patients with HBV-associated HCC than in those with non-HBV-associated HCC (r=0.373, p=0.001 for HBV-HCC; r=0.012, p=0.957 for non-HBV-HCC).

Conclusions: TERT and IL-6 are differentially expressed between male and female HCC patients, with a positive correlation only in male patients or those with HBV-associated HCC. These results give insight into the potential mechanism of TERT-IL-6 axis involved in gender disparity in liver carcinogenesis.

Keywords: Hepatocellular carcinoma, Telomere reverse transcriptase, Cytokines, Telomere

PE-101

Effects of Mesenchymal Stem Cell thorugh the Activation of Liver Sinusoidal Endothelial Cell in Hepatic Progenitor Cell

Seul Ki Han[1,2,3], Jin Suk Lee[2,3], Su Jung Park[2,3,4], Mi Ra Lee[2,3], Yoo Jin Lee[2,3], Soon Koo Baik[1,2,3], Moon Young Kim[1,2,3¶]

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea, [2]Regenerative Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea, [3]Cell Therapy and Tissue Engineering Center, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea, [4]Mitohormesis Research Center, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea

Background and Aims: The hepatic progenitor cell (HPC) is an innate stem cell in the liver and the main cell in liver regeneration. Induce that the proliferation and regenerative activity of HPC is the main issue in the liver regeneration field. Liver sinusoidal cells (LSECs) inactivation and stabilization are essential in accelerating the regression of fibrosis and inhibiting the progression of cirrhosis. LSEC also has been known to activate HPC through the Wnt-β-catenin signaling. However, the method to stabilize LSECs is not yet established. Therefore, we investigated the functional recovery of LSECs through mesenchymal stem cells (MSCs) and whether it can induce HPCs activation.

Methods: To evaluate the stabilization of LSEC by MSC, the recovery of fenestrae of LSECs was confirmed by Scanning Electron Microscope (SEM) after co-culture. Changes in various factors affecting the stabilization of LSEC were also confirmed by real-time polymerase chain reaction and Western blot. The specific cell markers of the isolated mouse LSECs and MSCs were confirmed by FACS. In addition, HPCs were cultured using the culture soup obtained by co-culture of LSECs and MSCs, and the activities of HPCs were analyzed.

Results: In human-derived MSC and LSCE co-culture, LSEC showed recovery of fenestrae with increased expression of VEGF, eNOS, HGF, Wnt2, and Wnt9b in LSEC compared with control. Also, when LSECs and MSCs isolated from mice were co-cultured, the expression of VEGF and HGF, which play an important role in maintaining the morphology of LSEC, increased. The expression of Wnt9b, which acts as an angiocrine factor in liver regeneration, was also increased. In the culture of HPC, when the soup obtained from LSEC during LSEC and MSC co-culture was added, an increase in HPC activity was observed compared to the control group. The proliferation of stem progenitor

cells was doubled in both 24 and 48 hours compared to the control group. Also, the expression of VEGF and Wnt2 increased in HPC at 24 hours, and the expressions of HGF, VEGF, and Wnt9b increased at 48 hours.

Conclusions: MSC showed the property that can induce stabilization (undifferentiated) LSEC. Stabilized and functionally recovered LSEC by MSC also induced the proliferation and increased the activity of HPCs and which suggests a possibility that MSC-based recovery of LSEC in hepatic fibrosis can be helpful in the promotion of liver regeneration through HPC activation.

Keywords: Liver cirrhosis, Regereration

PE-102

The Effect of Fecal Material Transplantation on Hepatic and Brain Diseases in a Non-Human Primate Model: Several Considerations for Future Application to Liver Disease Patients

Seok-Hwan Kim*[1], Bon-Sang Koo[2], In-Sang Song[1], Gwang-Sik Chun[1], Sun-Jong Han[1]

[1]Surgery, Chungnam National University, Republic of Korea, [2]National Primate Center, Korea Research Institution of Bioscience and Biotechnology, Republic of Korea

Aims: Recently, fecal microbiome transplantation (FMT) has been used to show effective treatment for human diseases. A preclinical animal model, a primate animal model most similar to humans, to study the overall physical effects of intestinal microflora and probiotics, and the direct effects on the liver and brain, is a very challenging and innovative task that is attempted for the first time in the world.

Methods: Acquisition of primates (9 animals) (Cynomolgus monkeys). Feces obtained from chronic diarrheal disease monkeys were transplanted into primates' transverse colons using FMT. Oral administration of human-derived probiotic strains to primates for six weeks (3 times). A sampling of liver tissue and portal vein blood through surgical treatment of primates. Microbiome analysis by performing 16S rRNA sequencing on fecal samples 2 and 6 weeks after fecal microbial transplantation and probiotics administration. Performing blood sampling from primates' femoral vein and hepatic portal vein. Hematological/blood biochemical analysis on obtained blood samples. Confirmation of inflammation induction through radiological analysis (18FDG PET-CT) analysis of primates. Metabolome analysis, such as fatty acids in the blood and hormones in the CSF.

Results: In blood samples from the portal vein, severe neutropenia was consistently observed in the subjects of fecal microbial transplant. The probiotics administration group observed no significant change in neutrophils. However, in the case of lymphocytes, a decrease or increase was observed for each individual. As a result of analysis before/after primate fecal microbial transplantation, a statistically significant increase in insulin, C-peptide, MCP-1, ACTH, and GH levels was observed. No changes in hormone levels were observed according to the fecal condition (diarrhea, normal stool) of fecal microbial transplantation. As a result of analysis before/after the administration of primate probiotics per oral, no significant changes in hormone levels were observed.

Conclusions: A significant change in the neutrophil/lymphocyte ratio in the portal vein is one of the considerations for the effect of FMT on the treatment of hepatocellular carcinoma. Hormonal changes in CSF may help control metabolic diseases (diabetes, hyperlipidemia) following immunosuppressive drugs in liver transplant patients. Considering that oral probiotics intake and the effect of FMT on primates are different, it will be necessary to view the route of administration when developing microbiome therapeutics in the future.

Keywords: Non-human primate, Fecal material transplantation, Liver disease

PE-103

Status of Blood Transfusion in Liver Surgery in Korean: A National Population-Based Study Using the National Health Insurance Service Database

Seonju Kim[1], Junghyun Yoon[2], Sunghee Hong[3,4], Boyoung Park[5]

[1]Department of Public Health Sciences, Hanyang University College of Medicine, Seoul, Korea, [2]Department of Preventive Medicine, Hanyang University College of Medicine, Seoul, Korea, [3]Department of Statistics and Data Science, Graduate School, Dongguk University, Seoul, Korea, [4]Institute for Health and Society, Hanyang University, Seoul, Korea, [5]Department of Preventive Medicine, Hanyang University College of Medicine, Seoul, Korea

Aims: This study aimed to investigate the current status of blood transfusion in liver surgeries in Korea for patient blood management.

Methods: : The study subjects were patients who underwent liver surgery from 2012 to 2020 in the National Health Insurance Service (NHIS) database.-Liver surgery was classified into hepatectomy and other liver surgery. Annual percent change (APC) and baseline analyses were performed according to each surgery's transfusion status and type.

Results: Of the 81,098 patients with liver surgery, 74,079 (91.3%) underwent hepatectomy, and 7,019 (8.7%) underwent other liver surgery. The proportions of the non-transfusion group versus any blood product group were similar (hepatectomy: 60.2% vs. 39.8, other liver surgery: 61.6% vs. 38.4%, respectively). Regarding the type of blood transfusion, red blood cell (RBC) transfusion was the most common (hepatectomy: 58.7%, other liver surgery: 50.6%, respectively). The number of patients who did not receive a blood transfusion in hepatectomy increased by an average of 6.2% each year. Among the hepatectomy patients, males accounted for 66.9%, and the mean age was higher in the transfusion group than in the non-transfusion group (any of blood product: 62.9, non-transfusion: 60.8). However, in other liver surgery, the mean age of the blood transfusion group was lower than that of the non-transfusion group (any of blood product: 57.6±16.5, non-transfusion: 61.4±12.5). The Charlson comorbidity index (CCI) score of transfused hepatectomy patients was higher at 5 than the non-transfused group.

Conclusions: Liver surgeries and blood transfusions in Korea are on the decline, but there are differences depending on the main disease and surgical method. Further studies on transfusion-related factors and prognosis after transfusion are needed in the future.

Keywords: Blood transfusion, Liver surgery, Patient blood management, Hepatectomy

PE-104

Machine Learning Models for Predicting Hepatocellular Carcinoma Development in Patients with Chronic Viral Hepatitis B Infection

Warissara Kuaaroon[1], Thodsawit Tiyarattanachai[1], Terapap Apiparakoon[2], Sanparith Marukatat[3], Natthaporn Tanpowpong[4], Sombat Treeprasertsuk[5], Rungsun Rerknimitr[5,6], Pisit Tangkijvanich[7], Roongruedee Chaiteerakij[5,6]

[1]Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [2]Department of Computer Engineering, Faculty of Engineering, Chulalongkorn University, Bangkok, Thailand, [3]Image Processing and Understanding Team, Artificial Intelligence Research Group, National Electronics and Computer Technology Center, Thailand, [4]Department of Radiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [5]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [6]Center of Excellence for Innovation and Endoscopy in Gastrointestinal Oncology, Chulalongkorn University, Bangkok, Thailand, [7]Center of Excellence in Hepatitis and Liver Cancer, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Aims: Chronic hepatitis B (CHB)-infected patients have varied risks for hepatocellular carcinoma (HCC). We developed machine-learning models to predict the short-term risk for developing HCC in CHB-infected patients to tailor the HCC surveillance interval.

Methods: Data from 7,593 follow-up visits of 3,187 CHB-infected patients between January 2008 and December 2017 were used to train the Extreme Gradient Boosted Tree models to predict the HCC occurrence within the next 3 and 6 months. The 3- and 6-month models (GB_3, GB_6) were constructed using clinical and laboratory features in combination with 3 input features: alpha fetoprotein (AFP) (GB^A), rate of AFP change (GB^R), and no AFP (GB^N). Model performance was evaluated using 10-fold cross validation and further validated with another independent cohort of 164 CHB patients during follow-up between January 2018 and December 2020.

Results: During the 26.4 months follow-up, 81 (2.54%) and 113 (3.54%) developed HCC. The models incorporating rate of AFP change provided the best performance. At a fixed specificity of 0.9, GB^R_3 provided the highest sensitivity of 0.86 (95% confidence interval (CI): 0.76-0.96), followed by GB^A_3 (0.8, 95% CI: 0.69-0.91) and GB^N_3 (0.74, 95% CI: 0.64-0.84), with AUROCs of 0.904, 0.906 and 0.86 respectively. The 6-month models followed the same trend. For the validation cohort in which 3 of 164 patients developed HCC, the GB^R_3, GB^A_3 and GB^N_3 models had specificities of 0.95 (95% CI: 0.93-0.96), 0.94 (95% CI: 0.92-0.96), and 0.87 (95% CI: 0.84-0.90), respectively, with similar sensitivities of 0.5 (95% CI: 0-1), while the GB^R_6, GB^A_6 and GB^N_6 models had specificities of 0.96 (95% CI: 0.94-0.98), 0.91, (95% CI: 0.89-0.94) and 0.85, (95% CI: 0.82-0.88), respectively, with similar sensitivities of 0.75 (95% CI: 0.33-1).

Conclusions: The machine learning models demonstrate good performance for predicting short-term HCC risk and may potentially be used for optimizing the surveillance interval for individual patients.

Keywords: Artificial intelligence, HCC risk prediction, Prediction model, HBV infection

[Liver Cancer: Non-Therapeutic Aspects]

PE-105

The Specificity of the Liver Cancer Marker PIVKA II Assay

Researcher: Oncologist: E. Tsend-Ayush[1] MD: D. Baasanjav[1], E. Oyuundalai[2]
Master of Medicine: D. Chinzorig[3]
Biomedical researcher: A. Tegshjargal[3], N. Nandintsetseg[3], B. Urangoo[3]
Advisor: Doctor of Medicine, Professor: O. Baatarkhu[2]
Supervisor: Doctor of Medicine, Associate Professor: J. Amarsanaa

MASLD, Mongolia

Aims: In Mongolia, liver cancer is not only the leading cause of cancer-related death, but also ranks first in the world in terms of the number of cases per 100,000 population. It is also the number one cause of death in the world because liver cancer is usually diagnosed at a late stage and a significant percentage because it is associated with cirrhosis of the liver, the PIVKA II liver cancer marker test has been localized, and it is important to detect liver cancer caused by the HBV, HCV at an early stage, which is prevalent in Mongolia, so the specificity of the test was compared with the specificity of the PIVKA II test performed in other countries. Research is currently not available in Mongolia, so it became a basis for comparative research.

Research Objectives: Identifying the unique quality of PIVKA II tests conducted in Mongolia in 2019-2022 and obtaining a suitable category for Mongolia.
• Log analysis changes by category
• Investigate liver cancer cells diagnosed with changes in abdominal ultrasound and abdominal CT scans in clients who have been tested.

Methods: Identifying the unique quality of PIVKA II tests conducted in Mongolia in 2019-2022 and obtaining a suitable category for Mongolia.

Results: From September 30, 2019 to December 2, 2022, Happy Veritas conducted liver tumor marker tests on a total of 2,492 people aged 12 to 92 years. If it is between 40-200, it is slightly increased, if it is between 200-1000, it is moderately increased, and if it is found more than 1000, it is considered as a group, and the diagnosis of hepatocellular carcinoma is confirmed. 1783 people or 71.55% of the total number of people tested were normal or 0-40 u/l, and among them, 0 people were diagnosed with hepatocellular carcinoma, and 1 person had colon cancer spread to the liver. 0% chance of having hepatocellular carcinoma. 583 or 23.3% of the total number of clients with test results of 40-200 or slightly increased, of which 38 or 6.7% of them were diagnosed with liver cancer by contrast-enhanced CT scan of the abdomen. Out of a total of 88 clients with a bio-marker test result of 200-1000 or moderately elevated, 47 patients or 53.4% were diagnosed with liver cancer. Liver cancer was diagnosed in 74 or 94:8% of 78 people whose PIVKA II test results were more than 1000 or very high.

Conclusions: The specificity of the Pivka-II test as a biomarker for the detection of hepatocellular carcinoma has been shown to be directly related to the clinical pathology of hepatocellular carcinoma.

Keywords: The specificity of the liver cancer marker PIVKA II assay, HCC, PIVKA2, The specificity of the liver cancer marker PIVKA II assay HCC

PE-106

Compliance of the Screening for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B or C

Hyunwoo Oh[1], Won Sohn[2], Yong Kyun Cho[2], Byung Ik Kim[2]

[1]Division of Gastroenterology, Department of Internal Medicine, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, [2]Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: This study aimed to investigate the compliance of the screening for hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis.

Methods: A cross-sectional study was conducted based on nationally representative samples from the Korean National Health and Nutrition Examination Survey 2007-2012. Of 50,405 participants, a total of 1,275 patients with chronic hepatitis B or chronic hepatitis C were included in the final analysis. We investigated compliance of HCC screening using ultranonography and serum alpha-protein. Univariable and multivariable logistic regression analyses were performed to evaluate the screening compliance associated risk factors such as age, sex, marital status, residential area, self-rated health status, education level, income status, private insurance for health care, alcohol and smoking.

Results: The mean age of 1,275 patients was 49.4 years and male was 51% (n=618). The compliance of HCC screening was observed in 508 patients (40%): within 6 months before the survey, 12 % (n=155); 6-12 months, 11% (n=134); >12 months, 17% (n=219). The multivariable analysis showed that compliance of HCC screening was significantly associated with age: 40-60 years (odds ratio [OR] 3.06 with 95% confidence interval [CI]: 2.26-4.15, p<0.001), age: >60 years (OR 2.92 with 95% CI: 1.93-4.42 p<0.001), self-rated health status: moderate (OR 1.42 with 95% CI: 1.07-1.89, p=0.016), self-rated health status: poor (OR 152 with 95% CI: 1.08-2.13, p=0.015), education: university or higher (OR 1.37 with 95% CI: 1.04-1.81, p=0.025), income: >50 percentile (OR 1.95 with 95% CI: 1.49-2.56, p<0.001) and private insurance for health care (OR 1.40 with 95% CI: 1.02-1.91, p=0.038).

Conclusions: Compliance of HCC screening was favorable in patients with older age, poor health status, higher education level, high income and private insurance for health care in Korea. These findings may be helpful to increase HCC screening and surveillance rate in patients with chronic viral hepatitis.

Keywords: Hepatocellular carcinoma, Chronic viral hepatitis, Surveillance

PE-107

Association of Physical Activity, including Amount and Maintenance, with Risk of Hepatocellular Carcinoma among Patients with Diabetes

Mi Na Kim[1,2], Wonkyung Han[3], Kyungdo Han[4], Jae Seung Lee[1,2], Hye Won Lee[1,2], Beom Kyung Kim[1,2], Seung Up Kim[1,2], Jun Yong Park[1,2], Do Young Kim[1,2], Sang Hoon Ahn[1,2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea, [3]Division of Gastroenterology, Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea, [4]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea

Aims: The association of physical activity (PA) with the risk of hepatocellular carcinoma (HCC) development in patients with diabetes remains unknown. We aimed to investigate the association of the amount and change of PA with the risk of HCC development in patients with diabetes.

Methods: Patients with type 2 diabetes who had undergone the health examinations in 2009 and 2011 were enrolled. In total, 1,439,152 patients were included in the final analysis. The level of PA was classified as inactive (<500 metabolic equivalent task [MET]-min/week), moderately active (500-1500 MET-min/week), and active (≥1500 MET-min/week). Change in PA was categorized as 'persistently no active PA', 'newly active PA', 'active PA quitter' and 'persistently active PA' according to the presence of active PA in 2009 and 2011.

Results: During median 5.2 years of follow-up, 22,686 patients developed HCC. When compared to inactive group, the risk of HCC development was significantly lower in moderately active (adjusted hazard ratio [aHR]=0.96, 95% confidence interval [CI]=0.93–0.99) and in active group (aHR=0.95, 95% CI=0.91–0.99). The patients in the 'persistently active PA' group had significantly lower risk of HCC development when compared to those in the 'persistently no active PA' group (aHR=0.91, 95% CI=0.84–0.98). Meanwhile, patients in the 'newly active PA' group and in the 'active PA quitter' group showed similar risk of HCC development to those in the 'persistently no active PA' group (all p>0.05).

Conclusions: In conclusion, PA showed a dose-response preventive effect against HCC in patients with diabetes. Patients in the 'persistently active PA' group showed significant reduction of HCC development compared to those in the 'persistently no active PA' group, regardless of intensity of PA.

Keywords: Physical activity, Hepatocellular carcinoma, Diabetes

PE-108

The Prognostic Efficacy of Biliary Drainage in HCC with Bile Duct Invasion: A Multicenter Retrospective Cohort Study with Propensity Score Matching

Keungmo Yang, Hyun Yang, Chang Wook Kim, Hee Chul Nam, Ji Hoon Kim, Ahlim Lee, U Im Chang, Jin Mo Yang, Hae Lim Lee, Jung Hyun Kwon, Soon Woo Nam, Soon Kyu Lee, Pil Soo Sung, Ji Won Han, Jeong Won Jang, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon, Hee Yeon Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

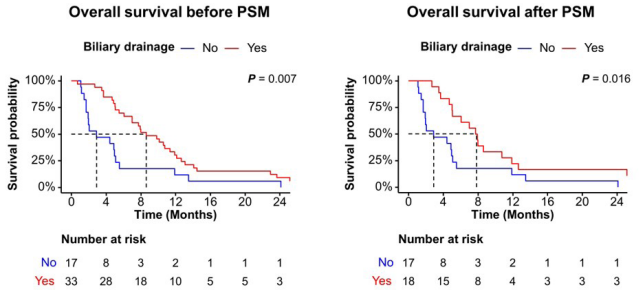
Aims: Bile duct invasion (BDI) is rarely observed in advanced hepatocellular carcinoma (HCC), which can lead to hyperbilirubinemia. Nevertheless, it remains uncertain whether pre-treatment biliary drainage is effective for HCC patients with BDI and obstructive jaundice. This research aims to investigate the impact of biliary drainage on the prognostic outcomes of these patients.

Methods: We retrospectively enrolled a total of 200 HCC patients

with BDI from multicenter cohorts. Patients without obstructive jaundice (total bilirubin level <3 mg/dL; n=99) or those who did not undergo HCC treatment (n=37) were excluded from the further analysis. Finally, 64 patients with obstructive jaundice (43 with drainage and 21 without drainage) were included, and propensity score matching (PSM) was conducted. The modalities of biliary drainage were percutaneous transhepatic biliary drainage or endoscopic retrograde cholangiopancreatography.

Results: Alpha-fetoprotein (≥400 ng/mL) and the duration between BDI diagnosis and HCC treatment were significantly different variables in baseline characteristics between the groups receiving biliary drainage and those without drainage in HCC patients with obstructive jaundice. The biliary drainage group showed better overall survival (Median OS, 8.9 vs. 2.9 months; p=0.007) and progression-free survival (Median PFS, 4.5 vs. 2.0 months; p=0.012) compared to the non-drainage group. Multivariate analysis demonstrated that biliary drainage was a significantly favorable prognostic factor for OS (Hazard ratio 0.44, p=0.013) and PFS (Hazard ratio 0.44, p=0.056). Furthermore, the biliary drainage presented the beneficial results in the first response evaluation after HCC treatment (p=0.001). Remarkably, there were similar results in OS (p=0.016) and PFS (p=0.033) after PSM analyses.

Conclusions: Biliary drainage is an independent favorable prognostic factor for HCC patients with BDI and obstructive jaundice. Therefore, this study suggests that biliary drainage should be contemplated in the treatment of advanced HCC patients with BDI for better survival outcomes.



Keywords: Hepatocellular carcinoma, Bile duct invasion, Biliary drainage, Propensity score matching

PE-109

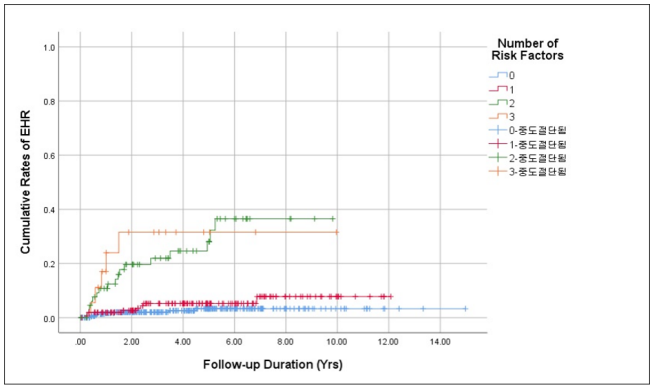
Clinical Characteristics and Risk Factors of Extrahepatic Recurrence after Hepatectomy of Hepatocellular Carcinoma without Intrahepatic Hepatocellular Carcinoma: A Multi-Institutional 15-Year Observational Study

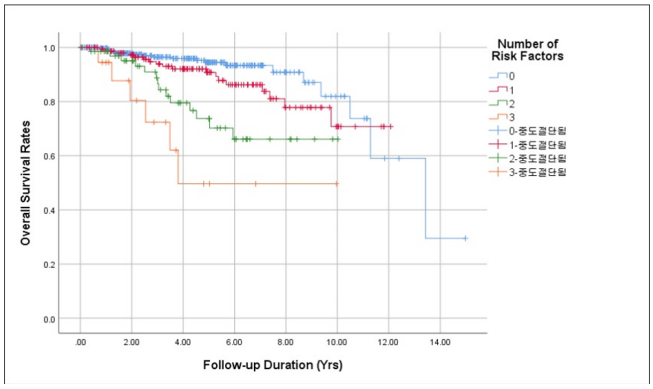
Ara Kyung, Jae Hyun Yoon

Department of Gastroenterology and hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea

Aims: Extrahepatic recurrence (EHR) is a well-known poor prognostic factor regarding hepatocellular carcinoma (HCC). Although EHR after hepatectomy of HCC may occur in high risk group of patients, little is known about EHR when there are no intrahepatic HCC. We investigated the clinical features and risk factors regarding EHR without remnant intrahepatic HCC at the time of EHR diagnosis.

Methods: Among 1,069 treatment-naive patients who underwent curative hepatectomy for HCC at four tertiary academic hospitals from January 2004 to December 2019, after exclusion of patients with intrahepatic recurrence (IHR) or EHR with IHR, and patients with insufficient clinical records, finally 569 patients were enrolled. The median follow-up duration was 3.91 years and multivariate analysis via Cox-regression was performed to identify the variables associated with EHR.





Results: Thirty-eight patients developed EHR after hepatectomy without remnant intrahepatic HCC during median follow-up duration of 1.04 years. Patients with EHR demonstrated significant early initial HCC recurrence than the patients without EHR; 1.73 vs. 4.43 years, respectively. On multivariate analysis, compared to patients without EHR, patients with EHR (without IHR) showed higher portion of venous/lymphatic involvement (HR 2.418, p=0.020), tumor necrosis (HR 2.592, p=0.009) and initial tumor stage beyond Milan criteria (HR=3.008, p=0.001). Also on analysis of factors related to survival after surgical resection of HCC, EHR was strongly associated with poor survival on multivariate analysis via Cox-regression (HR=14.044, p<0.001). Not only the cumulative rates of EHR correlated with the numbers of risk factors (Figure 1) but also the survival rates also exhibited step-wise relationship (Figure 2).

Conclusions: EHR without remnant viable HCC may occur in considerable number of patients after hepatectomy for HCC. Close monitoring for EHR is warranted in high risk group of patients despite of no HCC in liver.

Keywords: Extrahepatic recurrence, Hepatocellular carcinoma, Hepatectomy, Risk factor

PE-110

A Refined Prediction Model for Overall Survival in Patients Undergoing Transarterial Chemoembolization for Hepatocellular Carcinoma

Hae Lim Lee[1,2,3], Seok Hwan Kim[1,2,3], Hee Yeon Kim[1,2,3], Sung Won Lee[1,2,3], Myeong Jun Song[1,2,3]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]Korean Liver Cancer Study Group, [3]Ministry of Health and Welfare, Korea Central Cancer Registry

Aims: There is a lack of consensus on the optimal scoring system for patients with hepatocellular carcinoma (HCC) who underwent transarterial chemoembolization (TACE). In this study, we aimed to develop a new prediction model for overall survival (OS) in patients undergoing TACE as a first-line treatment and to evaluate its efficacy by comparing it to other currently utilized prediction models.

Methods: This study enrolled a total of 2,632 patients with HCC of Barcelona Clinic Liver Cancer (BCLC) stage A or B who underwent TACE between 2008 and 2017. The patients were randomly assigned to a training cohort (n=1,304) or a validation cohort (n=1,328). Independent predictors of OS were used to develop a prediction model.

Results: The median age of patients in the entire cohort was 63 years, with the majority having hepatitis B virus (56.6%) and being classified as Child-Pugh class A (82.4%). We developed a new prognostic model, called a TACE-prognostic (TP) scores, based on tumor burden (sum of the largest tumor diameter and tumor number), alpha-fetoprotein (AFP), and ALBI grade. Patients were classified into five risk groups according to TP score, with median survival significantly differentiated in both training and validation cohorts (p<0.001). The new model consistently outperformed other currently available models in both the training and validation datasets.

Conclusions: This newly developed TP scoring system has the potential to be a useful tool in identifying ideal candidates of TACE and predicting OS with favorable performance and discrimination. However, further external validation is needed to confirm its effectiveness.

Keywords: Transarterial chemoembolization, Hepatocellular carcinoma, Overall survival, Prediction

PE-111

Fiver-Year on-Treatment Parameters-Based Model Predicts Subsequent Hepatocellular Carcinoma in Entecavir/Tenofovir-Treated Patients

Yeonjung Ha[1,#], Jihye Lim[2,3,#], Young Eun Chon[1], Mi Na Kim[1], Joo Ho Lee[1], Kang Mo Kim[2], Ju Hyun Shim[2], Danbi Lee[2], Seong Gyu Hwang[1], Seungbong Han[4,*], Han Chu Lee[2,*]

[1]Department of Gastroenterology, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do 13496, South Korea; [2]Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea; [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul 06591, South Korea; [4]Department of Biostatistics, Korea University College of Medicine, 73, Goryeodae-ro, Seongbuk-gu, Seoul 02841, South Korea

Aims: Considering the lower risk of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients receiving long-term potent antiviral therapy, models predicting HCC after 5 years of therapy are needed.

Methods: We conducted a multicenter retrospective cohort study to construct and validate a model predicting HCC after 5 years of entecavir (ETV) or tenofovir (TFV) therapy for CHB. The endpoint was HCC after 5 years of ETV/TFV therapy. Information on age, sex, liver cirrhosis (assessed by diagnosis code and confirmed by clinical findings), and type of antiviral agent were obtained at baseline (initiation of ETV/TFV). Laboratory values were collected at baseline and at 5 years. Risk factors for HCC were identified using a random forest model and multivariable Cox regression in the training set. The final prediction model was validated using the test set.

Results: Among 7,542 patients, 345 (4.6%) developed HCC after 5 years of ETV/TFV therapy. HCC risk after 5 years of ETV/TFV therapy was increased by 4-fold in patients with liver cirrhosis than in those without cirrhosis at baseline. Furthermore, Platelet counts and Prothrombin time at 5 years, Age at baseline, and Sex were associated with increased risk of HCC and were incorporated to construct a prediction model, PPACS. PPACS had the best performance when compared to other prediction models in terms of a time-dependent area under the curve of 0.78 (95% confidence interval, 0.72–0.83) at 10-year of ETV/TFV therapy, a Brier score of 0.037, and an integrated Brier score of 0.013 in the test set.

Conclusions: The PPACS model provides a reliable assessment of HCC risk after 5 years of ETV/TFV therapy

Keywords: Chronic hepatitis B, Hepatocellular carcinoma, Prediction, Validation

PE-112

Factors Associated with Late HCC Detection in Patients with Chronic Liver Disease under Regular Surveillance

Sangmi Jang, Young-Joo Jin, Jin-Woo Lee, Dam Kwon, Jung Hwan Yu

Digestive Disease Center, Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea

Aims: Hepatocellular carcinoma (HCC) has a very poor prognosis with a 5-year survival rate of less than 20%, and early diagnosis is very important. However, despite regular check-ups for high-risk groups of HCC, there are a few cases in which it is discovered as a late-stage of HCC. Therefore, this study intended to investigate the characteristics of patients with delayed HCC detection during regular HCC surveillance.

Methods: Between January 2010 and December 2020, we analyzed patients with newly diagnosed HCCs who were screened for HCC by ultrasound or CT scan at least twice while following up for more than 1 year due to hepatitis B, hepatitis C, and chronic liver disease.

Results: The mean age of a total of 223 HCC patients was 70 years, of which 152 were male, accounting for 68.1%. Among them, 196 patients (87%) were diagnosed with BCLC stage 0 or A, while 27 patients (13%) were found to be in BCLC stages B and C. When classified according to the TNM criteria, 154 patients (69%) were in stage I and 69 patients (31%) were in stage II or higher. In this study, a multivariate analysis performed to identify risk factors for patients

diagnosed with late-stage HCC, CTP score was identified as a highly significant factor (p=0.002, HR 1.547, 95% CI 1.177 - 2.032), while the presence of cirrhosis, BMI, and sex had no significant effect.

Conclusions: We found that in patients with chronic liver disease who were screened regularly, patients with higher CTP scores were more likely to be diagnosed with HCC in late-stages. Therefore, although the presence of cirrhosis is also important for HCC surveillance, more careful attention is needed for patients with high CTP scores.

Keywords: HCC, surveillance, Advanced stage

PE-113

Surveillance of Hepatocellular Carcinoma Is Cost-Effective in Chronic Viral Hepatitis Patients in Korea

Young Youn Cho[1§], Hye-Lin Kim[2§], Eun Sun Jang[3], Dae Won Jun[4], Gi Hyeon Seo[5*], Hyung Jun Kim[1*]

[1]Department of Internal Medicine, Chung-Ang University Hospital, [2]College of Pharmacy, Sahmyook University, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, [4]Department of Internal Medicine, Hanyang University College of Medicine, [5]Health Insurance Review and Assessment Service

[§]These authors contributed equally to this work.

[*]Corresponding Author

Aims: Biannual hepatocellular carcinoma (HCC) surveillance of ultrasound (US) and alpha-fetoprotein (AFP) is recommended for chronic viral hepatitis and liver cirrhosis. However, there are little evidence supporting HCC surveillance in chronic hepatitis patients. In Korea, US was reimbursed in April 2018. After reimbursement, nationwide cost of the HCC surveillance program could be analyzed. This study aimed to check whether the HCC surveillance program was cost-effective using the nationwide cohort data.

Methods: We designed a Markov model to compare the expected costs and quality-adjusted live-years (QALYs), between biannual and annual surveillance compared to no surveillance, with a 20-year time horizon. The starting age of the cohort was set to 40 or 50 years. Transition probabilities and costs were obtained mainly from the National Health Insurance database. An incremental cost-effectiveness ratio (ICER) was calculated. Early HCC was defined by treatment methods.

Results: In liver cirrhosis patients, with starting age of 40, biannual and annual surveillance resulted in ICERs of $17,911 and $12,739 per QALY, respectively. When surveillance was restricted to chronic viral hepatitis patients without cirrhosis, with starting age of 40, biannual surveillance was marginally cost effective. Biannual and annual surveillance resulted with ICERs of $20,597 and $16,253 per QALY, respectively. After increasing the starting age to 50, both biannual and annual surveillance was cost effective, with ICERs of $12,288 and $9,742 per QALY respectively.

Conclusions: In Korea, HCC surveillance program was cost effective in most clinical scenarios for liver cirrhosis and chronic viral hepatitis patients.

Keywords: Hepatocellular carcinoma, Surveillance, Cost-effectiveness

PE-114

Comparison of Diagnostic Efficacy between ASAP Score and GALAD Score for Detection of Early-Stage Hepatocellular Carcinoma: A Multicenter Case-Control Study

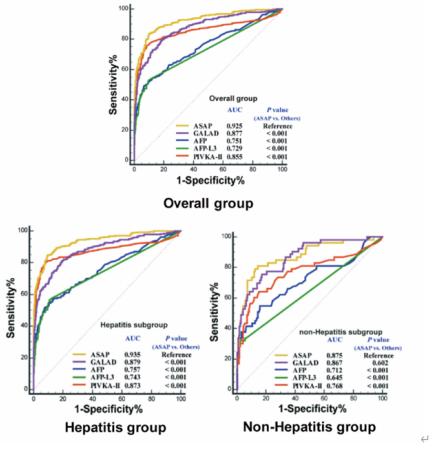
Wei Ouyang[1,2], Nan-Ya Wang[3], Ming-Da Wang[3], Li-Yang Sun[2,4], Yong-Kang Diao[2], Ming-Cheng Guan[5], Chao Li[2], Feng Shen[2], Guo-Yue Lv[3], Hong Zhu[5], Tian Yang[2,3]

[1]Hubei Cancer Hospital, Tongji Medical College, Huazhong University of science and Technology, Wuhan, Hubei, China, [2]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Navy Medical University, Shanghai, China, [3]Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, First Hospital of Jilin University, Changchun, Jilin, China, [4]Department of Graduate, Bengbu Medical College, Bengbu, Anhui, China, [5]Department of Medical Oncology, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

Aims: The ASAP score and GALAD score are emerging biomarker-based prediction tools for the detection of hepatocellular carcinoma (HCC), both utilizing age, sex, alpha-fetoprotein (AFP), and protein induced by vitamin K absence or antagonist-II (PIVKA-II) as predictive variables. The GALAD score additionally includes lens culinaris agglutinin-reactive fraction of α-fetoprotein (AFP-L3). This study aimed to compare the diagnostic efficacy of the ASAP score and GALAD score for detection of early-stage HCC.

Methods: A multicenter analysis of clinical data from 2018 to 2022, including patients with early-stage HCC (within Milan criteria, i.e., a single tumor ≤ 5 cm, or ≤ 3 tumors each ≤ 3 cm, without evidence of vascular invasion or extrahepatic spread) and chronic liver disease (CLD) controls, was conducted. AFP, AFP-L3, and PIVKA-II levels were assessed, and ASAP and GALAD scores calculated. Areas under the receiver operating characteristic curve (AUROC) were used to evaluate the diagnostic efficacy of both models.

FIGURE. Receiver operating characteristic curve comparisons between the ASAP model and the GALAD score, AFP, AFP-L3, and PIVKA-II for early-stage hepatocellular carcinoma detection in the overall group. AFP, α-fetoprotein; AFP-L3, lens culinaris agglutinin a-reactive fraction of α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II, AUC, area under the receiver operating characteristic curve.



Results: The analysis included 326 early-stage HCC cases and 911 controls. In an all-etiology early HCC cohort comparison, PIVKA-II showed the highest diagnostic efficiency (AUROC: 0.855) and sensitivity at 90% specificity (76.6%) among individual biomarkers. The

ASAP model demonstrated significantly better discriminatory potency compared to the GALAD score (AUROC: 0.925, 95% CI: 0.909-0.939 vs. 0.877, 95% CI: 0.858-0.895, p<0.001), with consistent results across subgroups based on liver disease etiology and presence of cirrhosis.

Conclusions: The ASAP score exhibited noninferior even better diagnostic efficacy compared to the GALAD score for early-stage HCC detection. Given its lower cost and comparable performance, the ASAP score may be a more favorable option for HCC screening or surveillance among high-risk populations, expanding the available options for clinical HCC screening strategies.

Keywords: Hepatocellular carcinoma, Biomarker, ASAP score, GALAD score, Early diagnosis, Milan criteria

PE-115

A Better Prognosis of Hepatocellular Carcinoma in Patientss with Chronic Hepatitis B Receiving Tenofovir Compared with Entcavir

Sung Won Chung, Hyun Jun Um, Jonggi Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Won-Mook Choi

Department of Gastroenterology, Liver Cancer, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

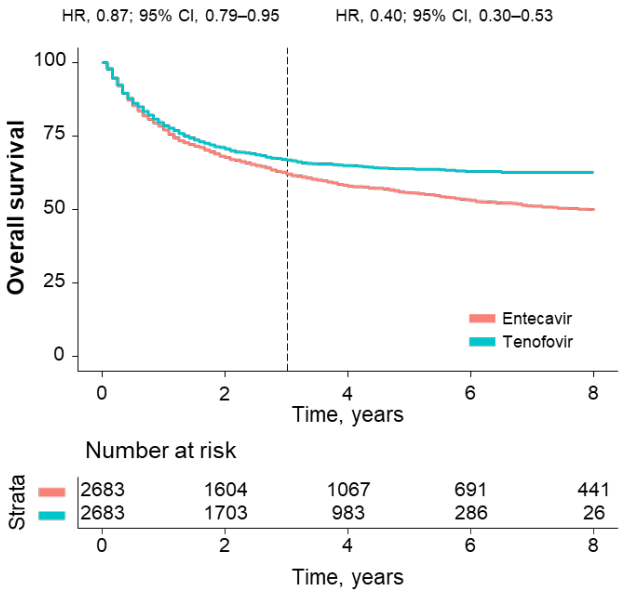
Aims: Whether tenofovir or entecavir has different effects on the prevention of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) in secondary and tertiary preventive settings remains controversial. This study was aimed to compare the long-term prognosis of HCC between tenofovir and entecavir in patients with chronic hepatitis B (CHB).

Methods: CHB patients who were diagnosed with HCC between November 2008 and December 2018 and were treated with either entecavir (n=3,469) or tenofovir (n=3,056) at a tertiary center in Korea were included. The effect of tenofovir vs. entecavir on the prognosis of HBV-related HCC was evaluated in a propensity score (PS)-matched cohort. Various predefined subgroup analyses were performed.

Results: The mean (SD) age was 54.6 (9.1) years, and 4,351 patients (81.1%) of the PS-matched cohort of 5,366 patients were male. During a median follow-up period of 3.0 years, entecavir-treated patients had a mortality rate of 43.0%, whereas tenofovir-treated patients had a mortality rate of 33.5%. Overall survival (OS) was better in tenofovir-treated patients compared with entecavir-treated patients (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73–0.88). The difference in OS probability between the two groups became more pronounced over time. The magnitude of the risk difference in OS after 3 years of HCC diagnosis (HR, 0.40; 95% CI, 0.30–0.53) was more prominent than that within 3 years (HR, 0.87; 95% CI, 0.79–0.95). In all subgroup analyses, tenofovir was associated with a better OS than entecavir, except for those with advanced or terminal stage HCC. For those who received curative-intent treatment, recurrence-free survival (HR, 0.83; 95% CI 0.73–0.95) and OS (HR, 0.63; 95% CI 0.50–0.79) were better with tenofovir compared with entecavir.

Conclusions: In patients with HBV-related HCC, tenofovir showed a better prognosis than entecavir, especially in those who survived longer.

Keywords: Antivirals, Hepatitis virus B



[Liver Cancer: Treatment]

PE-116

Proper Position of Single and Large (≥5 cm) Hepatocellular Carcinoma in Barcelona Clinic Liver Cancer stage

Hyo-Sin Kim

Department of Surgery, Chonnam National University Medical School and Hospital, Gwangju, Republic of Korea

Aims: Purposes: The purpose of this study was to evaluate proper position of single large hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer Stage system (BCLC).

Methods: The data was collected from the nationwide multicenter database of the Korean Liver Cancer Association. Patients with single large (≥5 cm) HCC was separated from BCLC A group and designated as group X. And remained BCLC Group A was renamed as Group A and BCLC Group B as Group B. Survival outcomes of propensity score-matched groups were compared.

Results: Among the 3965 randomly selected patients, Group X was 414, Group A (2787) and Group B (760). TriMatch analysis allowed us to obtain 116 well-balanced triplets. The 1-,3- and 5-year overall survival rates in the Group X was worse than Group A (91%, 71% and 48% *Vs* 90%, 78% and 64%, respectively; p<0.000). But it was not different compared to Group B (91%, 71% and 48% *Vs* 90%, 69% and 48%, respectively; p<0.09). In multivariable analysis, Group X, Group B, Age over 60 years, and prothrombin time international normalized ratio and Creatinine levels were independent predictors of worse overall survival.

Conclusions: Our findings suggest that Group X should be relocated to group BCLC B rather than BCLC A stage.

Keywords: HCC, BCLC, Survival outcome

PE-117

How to Cure Depression in Patients after Chronic Liver Disease or Liver Transplantation? Systematic Literature Review

Zulfa Saumia

Universitas Jambi, Indonesia

Aims: Depression is when a person experiences anxiety, feels uneasy, and so on. Depression can affect anyone, including patients with Chronic Liver Disease and Liver Transplants. This article aims to determine whether depression influences a person's long-term survival after Liver Transplantation (LT). What are the actions taken to reduce depression?

Methods: This abstract uses a literature study from PubMed using the keywords depression, chronic liver disease, and liver transplantation.

Results: The results of a literature review study found that patients prone to depression are Chronic Liver Disease (CLD) patients with chronic hepatitis C due to the use of interferon therapy. OLT patients with depression have a higher mortality rate than patients who are not depressed; appropriate use of anti-depressants will reverse this effect. Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are effective and generally safe in patients with CLD and OLT. Second, depressive symptoms and grades can be measured by the Back Depression Inventory (BDI) score during the first year post-transplant; depression usually occurs during the first year after L-TX (liver transplant). Third, the consumption of anti-depressants

Conclusions: It is hoped that in the future, researchers will be able to find out more about how bad the impact of depression is on daily life, identify early and developing depressive symptoms, or screening.

Keywords: Depression, Patients, Chronic liver, SLR

PE-118

Longterm Efficacy of HAIC with 3D-CRT for Unresectable Advanced Hepatocellular Carcinoma Complicated by Major Vascular Tumor Thrombosis

Joji Tani, Kei Takuma, Mai Nakahara, Kyoko Oura,Tomoko Tadokoro, Koji Fujita, Asahiro Morishita, Tsutomu Masaki

Department of Gastroenterology and Neurology, Kagawa University Faculty of Medicine, Japan

Aims: Hepatocellular carcinoma (HCC) complicated by portal vein tumor thrombus (PVTT) and/or inferior vena cava tumor thrombus (IVCTT) is associated with poor prognosis and has no established standard treatment. The aim of this study was to retrospectively evaluate the response rate, survival outcome, and adverse effects of hepatic artery infusion chemotherapy (HAIC) combined with three-dimensional conformal radiotherapy (3D-CRT) for intrahepatic tumor in patients with advanced HCC complicated by macrovascular invasion (MVI).

Methods: 49 patients with advanced HCC complicated by PVTT and/or IVCTT with sufficient residual hepatic function, regardless of the degree of disease progression were treated with this combination therapy modality from 2009 to 2022. HAIC consisted of cisplatin in lipiodol emulsion combined with 5-fluorouracil (New-FP). In principle, 3D-CRT was given at a total dose of 50 Gy in 25 fractions. After treatment completion, response to treatment, outcome, and adverse reactions were retrospectively analyzed.

Results: Of the 49 patients treated with NewFP + 3DCRT for MVI, 5, 26 and 8 patients had CR, PR, and SD, respectively. The treatment effect on MVI only was CR, PR, and SD in 5, 26, and 8 cases, respectively. The overall response rate was 67.4%, and the disease control rate was 84.8%. The median survival time was 12.9 months for all 49 cases. The MST for treatment response to MVI was 2.2 months for SD+PD patients and 22.0 months for CR+PR patients (p<0.001).The MST was 7.2 months for patients treated with NewFP plus 3DCRT for MVI and 22.0 months for those treated with systemic therapy after NewFP + 3DCRT for MVI (p=0.0123). The combination therapy was well tolerated, with no serious adverse reactions, except for reactivation of hepatitis B in 1 patient.

Conclusions: NewFP + 3D-CRT is demonstrated to be a safe and effective treatment option for patients with unresectable advanced HCC complicated by MVI.

Keywords: Advanced hepatocellular carcinoma, Major vascular tumor thrombosis, HAIC, 3DCRT

PE-119

Long-Term Outcomes and Evaluation of Hepatocellular Carcinoma Recurrence and Simple Scoring System for Prediction of Hepatocellular Carcinoma Occurrence after Hepatitis C Virus Eradication by Direct-Acting Antiviral Treatment: AKLD Group Study

Shungo Kimura[1], Joji Tani[1], Tomonori Senoh[2], Akio Moriya[3], Chikara Ogawa[4], Akihiro Deguchi[5], Teppei Sakamoto[6], Kei Takuma[1], Mai Nakahara[1], Kyoko Oura[1], Tomoko Tadokoro[1], Shima Mimura[1], Koji Fujita[1], Hirohito Yoneyama[1], Hideki Kobara[1], Asahiro Morishita[1], Takashi Himoto[7], Akemi Tsutsui[2], Takuya Nagano[2], Koichi Takaguchi[2], Tsutomu Masaki[1]

[1]Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University, [2]Department of Hepatology, Kagawa Prefectural Central Hospital, [3]Department of Gastroenterology, Mitoyo General Hospital, [4]Department of Gastroenterology and Hepatology, Takamatsu Red Cross Hospital, [5]Department of Gastroenterology, Kagawa Rosai Hospital, [6]Department of Internal Medicine, Yashima General Hospital, [7]Department of Medical Technology, Kagawa Prefectural University of Health Sciences, Japan

Aims: Direct acting antivirals (DAA) has improved the cure rate of HCV patients. However, the occurrence rate of hepatocellular carcinoma (HCC) and the long-term outcomes in patients with HCC recurrence after DAA treatment remains unknown.

Methods: At first, we aimed to identify predictors of HCC occurrence following DAA treatment. Among 1218 patients infected with HCV, 1,088 patients who achieved sustained virologic response and who had no history of HCC treatment were recruited between September 2014 and November 2018.

Results: The incidence of HCC was 0.61, 1.88, 2.82 and 3.71% at 6,

12, 18 and 24 months after treatment with DAA, respectively. The results of multivariate analysis identified age [hazard ratio (HR), 1.0729; p=0.0044] and α-fetoprotein (AFP) level after DAA treatment (HR, 1.0486; p=0.0486) as independent factors that may contribute to HCC occurrence following DAA treatment. By using these two factors, a novel scoring system (0-2 points) was established to predict HCC occurrence following HCV eradication by DAA treatment. The incidence of HCC at 2 years was 0.3% in the 0 points group, 6.27% in the 1point group and 18.37% in the 2points group. Secondly., we aimed to investigate the recurrence rates, recurrence factors, and prognosis of 130 patients who were treated with IFN-free DAA treatment after treatment for HCC. The recurrence rates of HCC were 23.2%, 32.5%, 46.3%, and 59.4% at 6, 12, 24, and 36 months, respectively. A multivariate analysis showed that palliative treatment prior to DAA treatment (HR=3.974, 95% CI 1.924–8.207, p=0.0006) and alpha-fetoprotein at sustained virological response 12 (HR=1.048, 95% CI 1.016–1.077, p=0.0046) were associated with independent factors for HCC recurrence (HCC-R). The 12-, 24-, and 36-month overall survival rates were 97.6%, 94.0%, and 89.8%, respectively. The 12-, 24-, and 36-month survival rates of the non-recurrence and recurrence groups were 97.7%, 97.7%, and 94.1% and 97.6%, 92.3%, and 87.9%, respectively (p=0.3404).

Conclusions: AFP level after DAA treatment and age at DAA administration were identified as independent predictors of HCC occurrence in patients that were treated with DAA. The scoring system that was established in the present study is simple and easy, and using pre-treatment factors may be a convenient tool to predict the risk of HCC occurrence in HCV-free patients following DAA treatment. Another study showed an improved prognosis regardless of recurrence rate, which suggests that DAA treatment in HCV patients should be considered.

Keywords: Direct-acting antivirals, Hepatocellular carcinoma recurrence, Hepatitis C virus, Alphafetoprotein

PE-120

Clinical Trial in Asian Patiens Liver Cancer: Sistematic Review

Ferza Alfath[1], Devi Yulia Rahmi[2]

[1]Department of Law, Alumnus Universitas Andalas, [2]Department of Management, Universitas Andalas, Indonesia

Aims: Liver cancer is cancer that originates from cells in the liver. This cancer can originate from liver cells or the spread of cancer cells from other organs, such as the intestine, skin, or breast (Halodoc, 2022). Primary liver cancer is a disease in which malignant (cancer) cells form in the liver tissue (National Cancer Institute, 2022). Clinical trials are experiments or observations in clinical research (Wiki, 2022). Clinical trials are also used in studying liver cancer in Asia. This study aim to development of liver cancer clinical trials in Asia.

Methods: This research uses a systematic review method. We collected articles from 2010-2023 from an electronic database, lens.org. The keywords used are Autoimmune Liver Disease and Asian Children. Then as many as three selected articles were reviewed to answer the purpose of this study.

Results: The Asian Liver Transplant Network (ALTN) is a strategic network of key opinion leaders in liver transplantation (LT) from Hong Kong, Japan, Indonesia, Singapore, South Korea, Taiwan, and the Philippines, which provides a platform for regular exchange to facilitate best clinical practice (Tan et al, 2019). Study from Chen et al. (2010) staging and treatment, clinical practice guidelines and recommendations for the design and conduct of clinical trials that have been developed primarily in the West cannot be used throughout the world without modification. Another study from Tan et al. (2019) there are notable differences in the indications and procedures for LT between Western and Asian settings.

Conclusions: Clinical trials on Asian Liver Cancer Patients began to develop in Hong Kong, Japan, Indonesia, Singapore, South Korea, Taiwan and the Philippines.

Keywords: Clinical trial, Asia, Systematic review, Liver cancer

PE-121

Prognostic Impact of the Progression of Lung Metastasis after the First Cycle of Atezolizumab plus Bevacizumab in Patients with Hepatocellular Carcinoma

Jiwon Yang, Jonggi Choi, Won-Mook Choi, Kang Mo Kim, Han Chu Lee, Ju Hyun Shim

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: Atezolizumab plus bevacizumab (Atezo/Bev) has been established as a standard first-line systemic treatment for advanced hepatocellular carcinoma (HCC). We aimed to investigate overall and organ-specific responses and their impact on survival in a specific group of patients with HCC and pulmonary metastases receiving Atezo/Bev.

Methods: This study included 73 consecutive HCC patients with at least one measurable lung metastasis and preserved liver function who received at least three 3-weekly cycles of Atezo/Bev at the Asan Medical Center, South Korea between 2018 and 2023. Responses assessment was based on RECIST v1.1: all metastatic lung lesions in present study were measurable. We defined "responders" as patients who achieved complete remission (CR) or partial remission (PR); and "progressors" as those with progressive disease (PD) at an initial evaluation after 3 cycles of treatment. The Kaplan-Meier method and Cox proportional model were used for overall survival (OS) analyses.

Results: Of the 73 patients, 46 (63.0%) had a single lung metastasis with/without intrahepatic lesions, and 55 (70.3%) and 25 (34.2%) were accompanied by intrahepatic HCC and vascular invasion of the tumors, respectively. The OS rate at 1-, 3-, 5-years were 78.2%, 59.9%, and 49.9%, respectively in the entire cohort with a median follow-up of 10.6 months. Of entire patients, 8 (11.0%) achieved overall response (0 CR and 8 PR), with 27 (37.0%) lung-specific responders (4 CR and 12 PR). Overall and lung-specific progressors were 20 (27.4%) and 25 (34.2%), respectively. Overall and pulmonary progressors had significantly lower survival rates than the counterparts (59.9% vs. 83.3% and 47.0% vs. 89.9% at 1 year; Ps<0.05), as was neither overall nor pulmonary responders. The lung-specific progressor and presence of macrovascular invasion were independent factors affecting survival, irrespective of other intra- and extra-hepatic status of the tumors.

Conclusions: Based on our data, pulmonary response to Atezo/Bev could help clinicians decide whether to continue the drug or switch to second-lines at an early phase of the initial therapy for HCCs with metastasis to the lung.

Keywords: Hepatocellular carcinoma, Atezolizumab plus bevacizumab, Lung metastasis

PE-122

Phytochemicals-Based Drug Designing for Liver Cancer: A Molecular Docking study

Preeti Puranik

Department of Bioinformatics & Computer Sciences, Shri Jain Diwakar Mahavidyalaya, India

Aims: The key focus of the present work is to search for plant-based phytochemical molecules which can efficiently interact with the targeted receptors responsible for the development and progression of liver cancer using molecular docking studies.
Liver Cancer has a major global health issue that consistently increases rates year over year. The primary cause of liver cancer is an unhealthy lifestyle and unhealthy eating habits. A new class of medications is anticipated to be developed as a result of the identification of novel biochemical pathways and molecular targets for pharmacological action in liver cancer-associated gene products. vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), c-mesenchymal-epithelial transition factor-1 (c-Met) and mammalian target of rapamycin (mTOR) targeting drugs have all received approval in recent years and are now being utilized in clinical settings.

Methods: We have screened 300 phytochemical molecules from plant sources against 5 potential hotspot targets: VEGFR, EGFR, FGFR, c-Met, and mTOR as Liver Cancer therapeutics. Our results show that among all molecules, 30 phytochemicals exhibit promising therapeutic potential for Liver Cancer treatment. A library of 300 phytochemicals was made by downloading drug structures from Pubchem based on available literature. These molecules were tested for possible therapeutic efficacy in response to selected target hotspot proteins of Liver Cancer using in-silico docking with the help of Maestro 12.4 version of Schrodinger Suite-2020-1. The crystal structure of 5 potential target proteins: VEGFR, EGFR, FGFR, c-Met, and mTOR domain was downloaded from the RCSB Protein data bank (RCSB-PDB).

Results: The MD simulation demonstrates a robust performance across all receptors targets. In addition, some predicted ligand-binding modes are moderately refined during MD simulations. These results systematically validate the reliability of a physics-based approach to evaluate receptor-phytochemical-based drug binding interactions. EGFR receptors domain protein shows the highest affinity (docking score -10.11) and binding energy (-104.7) with Delphinidin 3,5-diglucoside showing the best therapeutic efficacy in liver cancer.

Conclusions: Among the lead molecules Delphinidin 3,5-diglucoside, Baicalein, and Morphine have already been known for their anticancer properties, but the efficacy of Vitexin, IsoSkimmiwallin, Nodifloretin, Jaceosidin, and Nepetin; Delphinidin 3,5-diglucoside has high therapeutic efficacy for Liver Cancer. Our observation is further strengthened by the available literature showing promising therapeutic efficacy exhibited by these lead molecules in *in-vitro* and *in-vivo* cancer models.

Keywords: Liver cancer, Phytochemicals, Molecular Docking, Drug designing

PE-123

Developing of Artificial Intelligence on Liver Cancer: Systematic Review

Muhammad Irzaq, Devi Yulia Rahmi

Department of Music Education, Alumnus Universitas Negeri Padang, Department of Management, Universitas Andalas, Indonesia

Aims: Primary liver cancer is a disease in which malignant (cancer) cells form in the liver tissue (HBF, 2022). Along with these developments, technology is getting better at detecting liver cancer. Breakthroughs in artificial intelligence (AI) have inspired the development of algorithms in the cancer setting (Bakrani, 2023). Experts began to study how the use of AL in liver cancer. This study aims to see the development of AL in liver cancer.

Methods: Articles from 2010-2023 are collected from electronic databases. Then as many as ten selected papers were reviewed to answer the objectives of this study.

Results: The study results indicate that many researchers are starting to learn about AI and its relationship to liver cancer. The study by Xiong et al. (2023) shows that IB has experienced rapid development and has wide application in diagnosing and treating liver disease, especially in China. Meanwhile, a study by Bakrania et al. (2023) found that due to current limitations in the diagnosis and therapy of liver cancer due to the heterogeneity of the disease, insufficient knowledge of cell origin and barriers to delivery of specific non-toxic drugs to liver tumour cells, AI could revolutionize the field of liver cancer research. Finally, Sharma (2023) said that artificial intelligence tools could develop cancer treatments in less than 30 days. It goes a step further and predicts patient survival rates as well.

Conclusions: It can be concluded that AL and liver cancer are related and development, and researchers are increasingly studying this relationship.

Keywords: Artificial intelligence, Liver cancer, Review

PE-124

Financial Burden of Liver Cancer : Problem and Solution for Liver Cancer Patient

Fitri Kurnia

Department of Management, Faculty of economics, Muhammadiyah University of West Sumatera, Indonesia

Aims: Liver cancer is one of the deadliest cancers in Indonesia, therefore liver cancer is a health challenge that needs attention. In addition, liver cancer is a type of disease with high costs. This problem is certainly a challenge for cancer patients with low financial conditions, because they find it difficult to get treatment, especially those with severe liver cancer. Therefore, a solution is needed for liver cancer sufferers with financial difficulties, to get access to adequate health according to what they should get.

Methods: collected information from various articles, and made a selection with a focus category on financial solutions for liver cancer sufferers.

Results: Identification of financial difficulties needs to start when someone is diagnosed with cancer, health care providers need to communicate proactively with patients about cancer treatment costs, other costs and potential disruption to the work of cancer sufferers. Health clinics also need to connect patients with financial assistance services (Government Assistance, Pharmaceutical Patient Assistance Programs, Nonprofit Programs for Co-Pay Relief, Cancer Organizations, General Organizations). Cancer patients who have received a diagnosis should budget for their daily needs. You can use the Money Advice and Budgeting Service. Patients should also begin to open up with the help of friends and family, this is very useful in difficult times and helps them deal with financial difficulties. Patients and families can take advantage of charitable institutions, for financial difficulties.

Conclusions: There are several options that can be accessed by people with liver cancer in overcoming the problem of financial difficulties, these financial assistance services are in formal and informal forms. However, the most important is the financial identification performed by the patient after receiving a diagnosis of liver cancer, so that the financial condition and appropriate solutions can be mapped out.

Keywords: Liver cancer, Cancer organizations, High cost, Financial difficulties

PE-125

A Comparative Study of Atezolizumab plus Bevacizumab and Transarterial Chemoembolization plus Radiotherapy in Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombosis

Soon Kyu Lee[1,2], Jung Hyun Kwon[1,2*], Sung Won Lee[2,3], Hae Lim Lee[2,3], Hee Yeon Kim[2,3], Chang Wook Kim[2,4], Do Seon Song[2,5], U Im Chang[2,5], Jin Mo Yang[2,5], Soon Woo Nam[1,2], Seok-Hwan Kim[2,6], Myeong Jun Song[2,6], Ji Hoon Kim[2,4], Ahlim Lee[2,5], Hyun Yang[2,7], Si Hyun Bae[2,7], Ji Won Han[2,8], Heechul Nam[2,4], Pil Soo Sung[2,8], Jeong Won Jang[2,8], Jong Young Choi[2,8], Seung Kew Yoon[2,8]

[1]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3]Division of Hepatology, Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [4]Division of Hepatology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [5]Division of Hepatology, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [6]Division of Hepatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [7]Division of Hepatology, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [8]Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

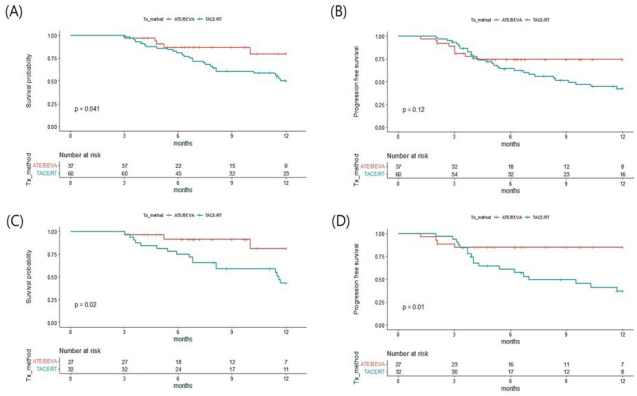
Aims: Immune checkpoint inhibitors (ICI), such as atezolizumab plus bevacizumab (Ate/Bev), have revolutionized treatment strategy for advanced hepatocellular carcinoma (HCC). Transarterial chemoembolization plus radiotherapy (TACE+RT) has also shown notable outcomes in HCC patients with portal vein tumor thrombosis (PVTT). In this study, we compared the treatment outcomes of Ate/Bev and TACE/RT in HCC patients with PVTT.

Methods: Between June 2016 and October 2022, we consecutively enrolled 855 HCC patients with PVTT who were treated at the Catholic University of Korea. Among them, 758 patients were excluded due to concurrent metastasis, treatment with tyrosine kinase inhibitors, ICI combined with RT, and follow-up loss within 3 months. Finally, 97 patients (37 in the Ate/Beva group and 60 in the TACE+RT group) were analyzed in our study. The primary outcome was one-year survival. Secondary outcomes were one-year progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Treatment outcomes were assessed using propensity-score matching (PSM) and multiple subgroup analyses.

Results: The median age was 59.1 years, and 87 patients were male. The majority of patients (n=73, 76.0%) had HBV infection. There were no significant differences in baseline characteristics between the Ate/Bev and TACE+RT groups. The TACE+RT and the Ate/Bev group had similar ORR (40.0% vs. 40.5%, p=1.000, respectively) and DCR (75.7% vs. 77.3%, p=0.957, respectively). The Ate/Bev group showed significantly higher one-year survival rate than the TACE+RT group (p=0.041, Figure A). The one-year PFS were marginally higher in the Ate/Bev group (Figure B). After PSM, the Ate/Bev group had better one-year survival (p=0.02) and PFS (p=0.01) than the TACE+RT group (Figure C,D). The Ate/Bev group still showed significantly higher one-year survival rate and marginally higher one-year PFS than the TACE+RT group in patients with extensive HCC burden. In Cox-regression analysis, the Ate/Bev group was the significant factor for better one-year survival (p=0.049).

Conclusions: The Ate/Bev treatment shows better clinical outcomes than the TACE+RT treatment in HCC patients with PVTT. Further studies with large number of patients are needed.

Keywords: Hepatocellular carcinoma, Portal vein thrombosis, survival, Progression free survival, Response, immune checkpoint inhibitors, Transarterial chemoembolization, Radiotherapy



PE-126

Therapeutic Efficacy of Radiofrequency Ablation with D-Sorbitol in Animal Livers

Ryosuke Imado[1], Asahiro Morishita[1], Kei Takuma[1], Mai Nakahara[1], Kyoko Oura[1], Tomoko Tadokoro, Koji Fujita, Joji Tani, Tsutomu Masaki

Department of Gastroenterology and Neurology, Faculty of Medicine, Kagawa University, Takamats, Kagawa, Japan

Aims: Radiofrequency ablation (RFA) is an effective, minimally invasive treatment for hepatocellular carcinoma. On the other hand, inadequate ablation may result in local recurrence. In fact, the size of coagulation necrosis is limited due to increased impedance by tissue fragments. D-sorbitol, which is a dielectric fluid, is a perfusate in transurethral resection of the prostate and used as lavage for removing tissue fragments. Therefore, the aim of this study is to investigate if the use of D-sorbitol in RFA can increase the coagulation range and provide a better therapeutic effect using animal liver.

Methods: Using a pig liver and a live dog liver, RFA with or without D-sorbitol were performed in five different liver sites. After RFA needle insertion, up to 20 ml of 3% D-sorbitol was slowly injected into the lesion from the same puncture site during RFA procedure. RFA was terminated when the impedance threshold was exceeded.

Results: The RFA group with D-sorbitol had significantly a larger volume of coagulated necrotic areas and a greater total energy content than that without D-sorbitol. No significant complications such as hemorrhage or injury were observed in the RFA group with D-sorbitol in the living dog liver. In addition, RFA has been performed without serious complications.

Conclusions: RFA with D-sorbitol might be a safe and effective therapeutic method for the treatment of early stage of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation, D-sorbitol

PE-127

A Case of Seeding along the Needling Tract Following Radiofrequency Ablation for Hepatocellular Carcinoma

Ga Ram You[1], Su Hyeon Cho[2], Jae Hyun Yoon[2], Sung Kyu Choi[2], Sung Bum Cho[1]

[1]Department of Gastroenterology and hepatology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea, [2]Department of Gastroenterology and hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea

Aims: Radiofrequency ablation (RFA) is an important tool in the treatment for early hepatocellular carcinoma (HCC). The complication of tract seeding is known to occurs roughly up to 1.7% of RFA procedures. There are quite a few reported cases of tract seeding of RFA, but no recommended treatment has been established yet. We would like to introduce a case that maintains a remission state through combination therapy of trans-arterial chemoembolization (TACE) and surgical resection, in a patient with intrahepatic HCC and RFA tract seedings.

Methods: A 57-year-old man, who followed up for chronic hepatitis B, liver cirrhosis and hepatocellular carcinoma, was found newly detected HCCs in his follow-up computer tomography (CT) image.
He received radiofrequency ablation for two HCCs of S4/5 in August 2015, and trans-arterial chemoembolization for intrahepatic recurred tumor of S4/5 in April 2020.
After 6 years from RFA and 1 year from TACE, three HCCs in S4a and S4b/S5, and metastatic nodules in right chest wall and perihepatic areas. (Figure 1.)
Coincidentally, these metastatic nodules were developed along the tract where the RFA needle passed in 2015.

Results: We treated this patient with surgery and TACE. First, for three intrahepatic HCCs in S4 and S5, we proceeded TACE. And for metastatic nodules in right chest wall and perihepatic area, we requested resection to department of hepato-biliary-pancreatic surgery and the nodules were resected with laparotomy. (Figure 2.)
A year later, no intrahepatic or extrahepatic recurrent tumors have been found in follow-up images.

Conclusions: Needling tract seeding occurs about upto 1.7% of RFA and upto 2.7% of percutaneous liver biopsy. To reduce the incidence of this complication, it is recommended to use oblique approaches to subcapsular tumors, minimize the number of needle insertions, and ablate the needle tract upon exit. After successful procedure, long-term surveillance follow-up is recommended, as implanted tumors may take months or years to develop. The tract seeding can be cured with local treatment such as surgical excision, and it does not have any reduction in survival if detected early and treated appropriately.

Keywords: Needle tract seeding, Hepatocellular carcinoma, Radiofrequency ablation

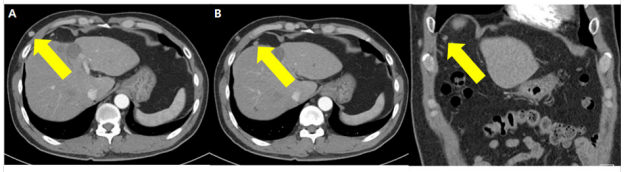


Figure 1. Extrahepatic metastases along the needling tract following radiofrequency ablation for hepatocellular carcinoma.
A : 1.1cm sized enhancing metastatic nodule in right chest wall. (arrow)
B : 1cm sized enhancing metastatic nodule in perihepatic area. (arrow)
C : 0.9cm sized enhancing metastatic nodule in perihepatic area. (arrow)

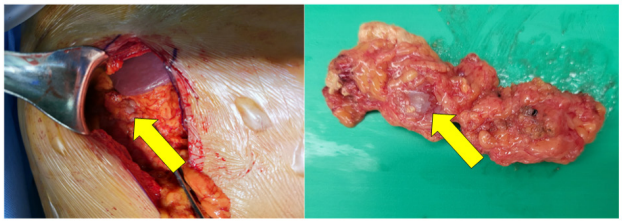


Figure 2. Omental mass (seeding of hepatocellular carcinoma) excision.
A : intraoperative image of omental mass. (arrow)
B : postoperative image of excised omental mass. (arrow)

PE-128

A Case of Thrombotic Event Associated with Long-Term Usage of Combination Therapy of Atezolizumab plus Bevacizumab in Advanced Hepatocellular Carcinoma Patient

Ga Ram You[1], Su Hyeon Cho[2], Jae Hyun Yoon[2], Sung Kyu Choi[2], Sung Bum Cho[1]

[1]Department of Gastroenterology and hepatology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea, [2]Department of Gastroenterology and hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea

Aims: Therapy with atezolizumab plus bevacizumab is the new standard treatment option for advanced hepatocellular carcinoma (HCC) currently. In advanced HCC patients, gastrointestinal disorders and bleeding are well known common adverse reaction to the combination therapy of atezolizumab and bevacizumab, but thromboembolism is a less known side effect. There are several known cases in patients using combination therapy of atezolizumab and bevacizumab in colon cancer, but few reports have been reported in HCC. Herein, we would like to report a thrombotic event that occurred in HCC patient with long term combination therapy of atezolizumab and bevacizumab.

Methods: A 77-year-old male was diagnosed with infiltrative HCC in right hepatic lobe and tumoral thrombosis in right portal vein. He experienced 23 cycles of systemic therapy of atezolizumab and bevacizumab after respectively 8, 6 courses of transcatheter arterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) in sequence. His history included liver cirrhosis associated with hepatitis virus C of genotype Ib, which had been eradicated by 24 weeks of Daclatasvir plus Asunaprevir and then virologic response had been sustained. He visited the emergent department suffering painful swelling of left lateral neck and left chest wall at 9 days after 23rd cycle of a combination therapy with atezolizumab and bevacizumab. He also presented skin redness, limitation of movement due to pain of the site, and fever with chillness (Figure 1A, B).

Results: The chest CT angiography revealed diffuse venous thrombosis of left brachiocephalic vein, left subclavian vein, and left internal jugular vein (Figure 1C, D). On the same chest CT, edematous change of left chest wall was shown. We planned left upper extremity venography with thrombectomy. Through the left cephalic vein approach, the venogram revealed short segmental severe stenosis in the left brachiocephalic vein, segmental occlusion in the left internal jugular vein, and thrombotic filling defects in the left subclavian and axillary veins. Aspiration thrombectomy and mechanical thrombectomy using a Forgarty balloon (Figure 2A), balloon angioplasty was performed repeatedly (Figure 2B, C). post procedural venogram showed remained stenosis with turbulent blood flow, so the intervention team decided to insert 14 x 6 mm Smart stent. Completion venography demonstrated recanalization of the stenotic vessels (Figure 2D). After the procedure, the patient was prescribed daily 30mg edoxaban anticoagulation, and then painful swelling gradually improved. Finally, he was discharged without any complications.

Conclusions: Bevacizumab is a monoclonal antibody targeting VEGF which plays an essential role in developmental angiogenesis of cancer cells. The humanized anti-VEGF monoclonal antibody bevacizumab has been used as a key agent in cancer therapy. In clinical trials and reported cases of bevacizumab, several adverse events have been observed. Including bleeding, the most commonly observed adverse events were hypertension, proteinuria, and thrombosis, especially after the extensive use of this agent. While thromboembolic events in patients with metastatic colon cancer or lung cancer treated with bevacizumab were reported, there was no reported case of thrombotic events associated with bevacizumab in advanced HCC patients. In our case, quite a number of times using bevacizumab was thought to be associated with the massive venous thrombosis. If thromboembolic events developed during the combination therapy of bevacizumab and atezolizumab, it would be treated by anticoagulation with or without thrombectomy as in our case. Although our report is the first case of thromboembolic event developed in an advanced HCC patient treated with bevacizumab, hepatologists who treat advanced HCC patients should be aware of the toxicity associated with bevacizumab.

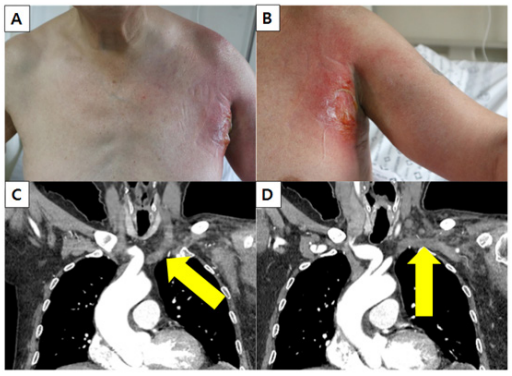


Figure 1. Initial clinical imaging of patient.
A: Erythema and swelling in left arm and chest wall. B: Skin abrasion, erythema and swelling with early necrotic change in left chest wall. C: Diffuse thrombosis in left internal jugular vein. D: Diffuse thrombosis in left brachiocephalic vein.

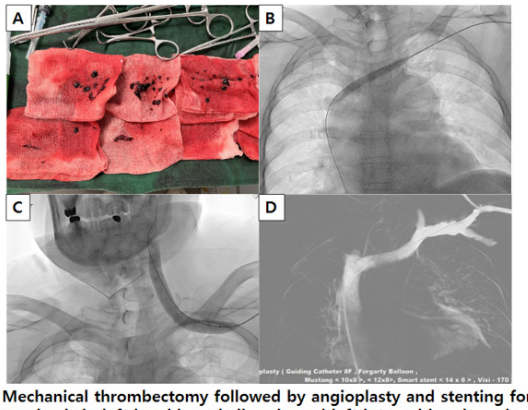


Figure 2. Mechanical thrombectomy followed by angioplasty and stenting for venous thrombosis in left brachiocephalic vein and left internal jugular vein.
A: Removed thrombosis by aspiration and mechanical thrombectomy. B: angioplasty left brachiocephalic vein. C: angioplasty at left internal jugular vein. D : Post angiopla and deployment of smart stent.

Keywords: Thromboembolism, Hepatocellular carcinoma, Atezolizumab, Bevacizumab

PE-129

Effectiveness and Safety of Sorafenib 400 mg Initial Dose Compared with Sorafenib 800 mg Initial Dose on Survival in Patients with Advanced and Intermediate Stage Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

Roland Helmizar[1], Juferdy Kurniawan[2], Alvina Widhani[3]

[1]Faculty of Medicine, Baiturrahmah University, Padang, West Sumatera, Indonesia, [2]Division of Hepatobiliary, Department of Internal Medicine, dr. Cipto Mangunkusumo National Central General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia, [3]Division of Allergy and Immunology, Department of Internal Medicine, dr. Cipto Mangunkusumo National Central

General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Aims: Sorafenib is a multi-tyrosine kinase inhibitor that has been shown to improve survival in patients with advanced and intermediate-stage hepatocellular carcinoma (HCC). Based on the search to date, there is quite a number of studies evaluating the effectiveness and safety of sorafenib 400 mg compared to sorafenib 800 mg on the survival of patients with advanced and intermediate HCC; however, the previous studies have shown varying results. This study aims to determine the effectiveness of sorafenib 400 mg initial dose compared with sorafenib 800 mg initial dose on survival in patients with advanced and intermediate HCC and its side effects in both groups.

Methods: We performed a systematic search of Randomized Controlled Trials and Non-Randomized Studies of Interventions from PUBMED, EMBASE, EBSCO, PROQUEST, snowballing, global index medicus, GARUDA, SINTA, and several digital libraries of universities in Indonesia until April 30, 2021. Of the 603 articles, there were 5 NRSI studies that met the eligibility criteria. Data were analyzed using Review Manager 5.4.1.

Results: Sorafenib 400 mg initial dose was significantly more effective on overall survival compared to sorafenib 800 mg initial dose in patients with advanced and intermediate HCC (HR 0.84; 95% CI 0.71–0.98; p=0.03). There was no difference in the overall incidence of adverse events to various degrees between the two groups (pooled OR 0.93; 95% CI 0.67–1.30; p=0.68).

Conclusions: Sorafenib 400 mg initial dose has a better effectiveness on overall survival with no significant difference in the incidence of adverse events compared to sorafenib 800 mg initial dose in patients with advanced and intermediate HCC.

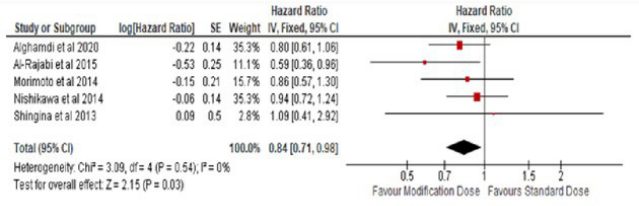


Figure 3. Effectiveness of sorafenib 400 mg initial dose on overall survival

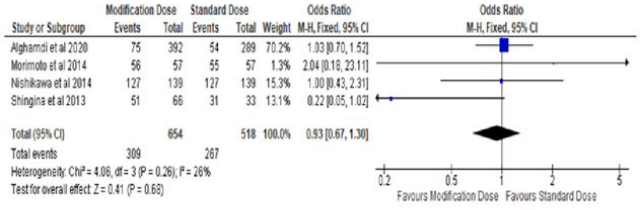


Figure 4. Odds ratio for overall side effects between two groups

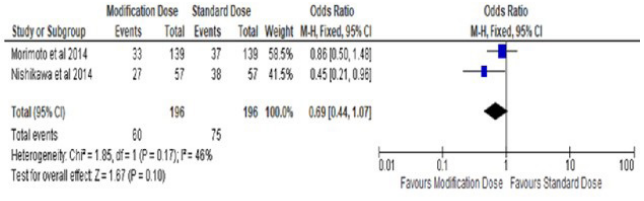


Figure 5. Odds ratio for severe (grade 3 or higher) side effects between two groups

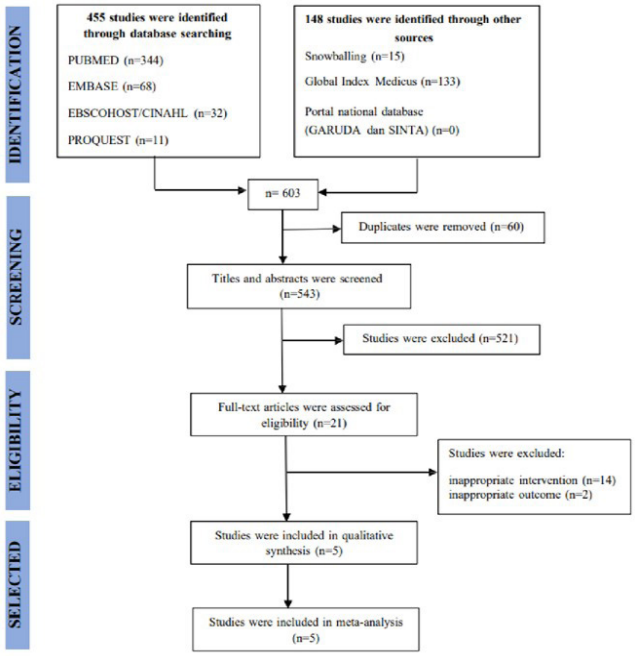


Figure 1. Flowchart of study selection process

Keywords: Hepatocellular carcinoma, Sorafenib, Overall survival, Side effects

PE-130

Sorafenib versus Lenvatinib after Atezolizumab/Bevacizumab Failure in Patients with Advanced Hepatocellular Carcinoma: A Real-World Multicenter Study

Young Eun Chon[1*], Dong Yoon Kim[2*], Mina Kim[2], Jaekyung Cheon[3], Jun Yong Park[2], Yeonjung Ha[1], Joo Ho Lee[1], Kwan Sik Lee[1], Hong Jae Chon[3#], Do young Kim[2#]

[1]Department of Gastroenterology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea, [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [3]Department of Medical Oncology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea

Aims: Atezolizumab plus bevacizumab (ATE+BEV) regimen showing favorable clinical response has become the first line recommended systemic therapy in patients with advanced hepatocellular carcinoma (HCC). However, data on sequential regimen after progression from ATE+BEV therapy are scarce.

Methods: This multicenter, retrospective study assessed clinical outcomes of patients with advanced HCC who received subsequent systemic therapy after progression on ATE+BEV therapy between May, 2020 and December, 2022. Treatment response was assessed using the Response Evaluation Criteria in Solid Tumors (version 1.1.).

Results: Among 133 patients enrolled, 39 patients were treated with lenvatinib, 86 patients were treated with sorafenib, and 8 patients were treated with regorafenib after ATE+BEV failure. The median age was

62 years, with male predominance (88.0%). There was no significant difference in the objective response rate between the lenvatinib and sorafenib groups (5.6% vs. 7.4%; p=0.784). However, both progression free survival (value [95% confidence interval {CI}]; 3.5 [3.6-4.4] months vs. 1.8 [1.5-2.1] months; p=0.001) and overall survival (value [95% CI]; 10.3 [6.9-13.7] months vs. 6.1 [3.9-8.3] months; p=0.036) was significantly higher in lenvatinib group compared to sorafenib group.

Conclusions: Lenvatinib compared to sorafenib treatment as the second-line therapy for unresectable HCC after ATE+BEV failure showed more favorable clinical efficacy in the real-world setting. Future studies with a larger sample size and longer follow-up are needed to validate this result.

Keywords: Atezolizumab, Bevacizumab, Second-line, Hepatocellular carcinoma

PE-131

The Efficacy and Safety of Atezolizumab & Bevacizumab in Patients with Unresectable Hepatocellular Carcinoma: The Real World Data

Sung Hwan Yoo, Hyun Woong Lee, Jung Il Lee

Department of Internal Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea

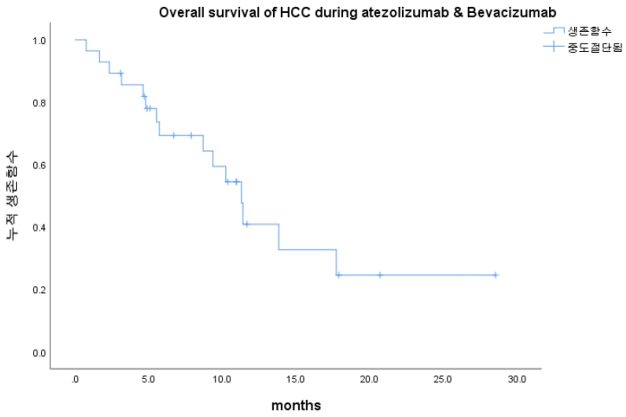
Aims: Treatment responses of unresectable hepatocellular carcinoma (HCC) remain unacceptably low and treatment modalities are limited. After the IMbrave 150 trial was announced, there are still few published data on the atezolimumab and bevacizumab in South Korea. We analyzed the efficacy and safety of atezolizumab & bevacizumab based on real world data.

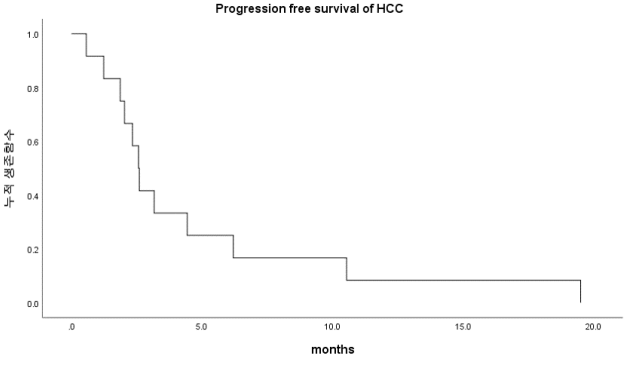
Methods: In retrospective cohort study, data on 28 patients with unresectable HCC, with Child-Pugh (CP) scores of 5-8, were collected from a university hospital between September 2020 and October 2022. All patients were treated with 1200mg of atezolizumab plus 15mg per kilogram of body weight of bevacizumab intravenously every 3 weeks.

Results: From 28 patients with unresectable HCC, 92.8% were classified as Child-Pugh (CP)-A, 64.2% as Barcelona Clinic Liver Cancer (BCLC)-C. The median overall survival (OS) and time to progression (TTP) were 11.2 months, and 3.6 months in the atezolizumab & bevacizumab group. In univariate analysis, operation, European Cooperative Oncology Group, sodium level, PIVKA-II, hepatic encephalopathy, ascites, Child-Pugh score group, maximum tumor size, were significant prognostic factors of OS (p = 0.049, 0.011, 0.004, 0.013, 0.049, 0.005, 0.013). In multivariate analysis, PIVKA-II, hepatic encephalopathy, Child-Pugh score group, maximum tumor size were significant prognostic factors of OS (p = 0.007, 0.002, 0.002, 0.008), Major complications included hyperbilirubinemia (44.8%), ALT elevation (34.5%), liver failure (14.2%), infection (2.1%), cerebral haemorrhage (0.04%), and hematuria (0.04%).

Conclusions: For managing unresectable HCC, atezolizumab & bevacizumab may be a valuable and safe treatment modality, but long-term follow-up and large scale studies are needed in the future.

Keywords: Atezolizumab, Bevacizumab, Hepatocellular carcinoma





PE-132

In-Depth External Validation of Subclassification System of Hepatocelluar Carcinoma with Macroscopic Vascular Invasion Treated with Combined Transarterial Chemoembolization and Radiotherapy as a First-Line Treatment

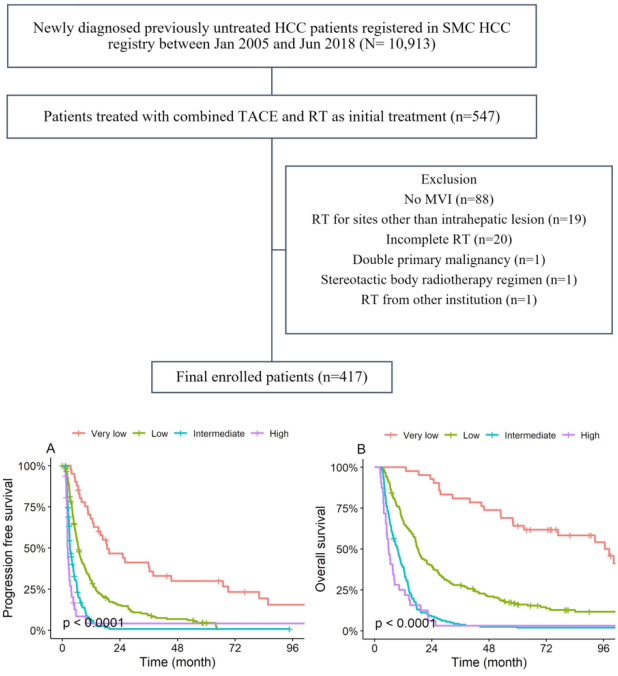
Jeong Il Yu[1], Hee Chul Park[1], Hyunju Shin[1], Hyunki Park[1], Sung Wook Shin[2], Sung Ki Cho[2], Dongho Hyun[2], Myung Ji Goh[3], Moon Seok Choi[3], Boram Park[4], Sang Min Yoon[5], Jinhong Jung[5]

Departments of [1]Radiation Oncology, [2]Radiology, [3]Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, [4]Biomedical Statistics Center, Research Institute for Future Medicine, Samsung medical Center, Seoul, Korea, [5]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: The present study aimed to validate the performance of a previously proposed subclassification model to predict prognosis after combined transarterial chemoembolization (TACE) and external beam radiotherapy (RT) for hepatocellular carcinoma (HCC) with macrovascular invasion (MVI) in an independent cohort that received the same first-line treatment for the patients with the similar disease extent characteristics, and analyzed the progression patterns as well as progression-free survival (PFS).

Methods: This study was conducted using prospectively collected data from the XXXXX HCC registry for newly diagnosed, previously untreated HCC between 2005 and 2018. Finally, 417 patients who sat-

isfied the eligibility criteria were included and analyzed.



Results: The median PFS and overall survival (OS) were 5.2 and 13.9 months, respectively. Similar to a previous study, subclassification of patients into very low-, low-, intermediate-, and high-risk groups showed a median OS of 98.4, 18.3, 9.7, and 5.8 months, respectively (p<0.001). Additionally, subclassification of patients into the very low-, low-, intermediate-, and high-risk groups showed median PFS of 18.7, 6.7, 3.3, and 2.3 months, respectively (p<0.001). Overall, intrahepatic progression was the most common pattern of progression; however, extrahepatic progression was more common in the intermediate- and high-risk groups.

Conclusions: The previously proposed subclassification model was successfully validated in an independent cohort. Treatment modification should be considered in the intermediate- and high-risk patient groups because extrahepatic progression is common after combined TACE and RT.

Keywords: Hepatocellular carcinoma, Macrovascular invasion, Radiotherapy, TACE

PE-133

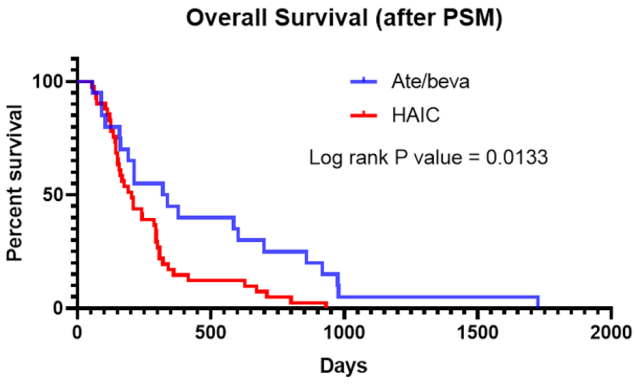
Comparative Analysis of Combination Therapy (Atezolizumab + Bevacizumab) and Hepatic Artery Infusion Chemotherapy in Unresectable Hepatocellular Carcinoma: A Multi-Center Study

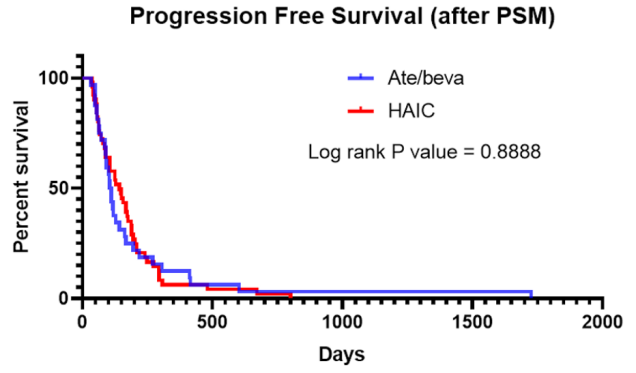
Ji Hoon Kim[1], Suho Kim[2], Ho Jong Chun[2], Jung Suk Oh[2], Chang Ho Chun[3], Ji Won Han[1], Jeong Won Jang[1], Jong Young Choi[1], Seung Kew Yoon[1], Pil Soo Sung[1]

[1]Department of Gastroenterology and Hepatology, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [2]Department of Radiology, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea, [3]Department of Radiology, Eun pyeong St Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Aims: In our institute, patients who are not feasible for or cannot afford the first-line systemic chemotherapy, hepatic artery infusion chemotherapy (HAIC) is proposed and can be used for treatment. Up to date, to our knowledge, there has been no study regarding the comparison between combination therapy, atezolizumab and bevacizumab(AB), and HAIC in advanced hepatocellular carcinoma(HCC) patients. The purpose of this study was to compare the prognosis and characteristics of the advanced HCC patients treated with the first-line combination therapy and hepatic artery infusion chemotherapy.

Methods: We retrospectively assessed 179 patients treated with HAIC and 72 patients treated with AB combination therapy between January 2018 and January 2023. Firstly, we assessed the overall survival (OS), progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR) between patients who received AB combination therapy and HAIC. Due to baseline characteristic differences between the two groups, we also analyzed results with propensity score matching (PSM) method.





Results: When we compared the baseline characteristics of the enrolled patients, we found that there were significant differences in BCLC stage, Child Pugh class, serum AFP level, tumor size, portal vein invasion and distant metastasis. Before PSM, our analysis revealed that HAIC-treated patients' PFS was significantly superior to AB-treated patients (p<0.05). However, there was no significant difference in overall survival between the two groups (p=0.1056). Before PSM, there was no significant difference between the ORR between the two groups (p=0.137) but there was a significant difference in DCR (p<0.05). We analyzed our data using PSM method with the following

factors: sex, age, etiology, ECOG performance status, BCLC, Child-Pugh scores and metastasis. (Caliper=0.2) After PSM, our data revealed that there was no significant difference in PFS between patients who received AB combination therapy and HAIC therapy (p=0.8888) but there was significant difference in overall survival; patients who received AB combination therapy had significantly better overall survival than those who received HAIC therapy. In addition, after PSM, there were no significant differences between ORR and DCR.

Conclusions: According to our data, after adjusting for bias that could occur due to confounding variables by PSM method, patients treated with AB therapy has a significantly longer OS than patients treated with HAIC. Due to the retrospective nature of this study, more studies will be needed to elucidate this phenomenon.

Keywords: Hepatocellulcar carcinoma, Atezolizumab+bevacizumab, Hepatic artery infusion chemotherapy, Prognosis

PE-134

Survival Prediction Model for Patients with Hepatocellular Carcinoma and Extrahepatic Metastasis Based on XGBoost Algorithm

Jihye Lim[1], Hyeon-Gi Jeon[2], Yeonjoo Seo[1], Moonjin Kim[3], Ja Un Moon[4], Se Hyun Cho[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, [2]Core platform team, SOCAR Incorporated, Seoul, Republic of Korea, [3]Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, [4]Department of Pediatrics, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

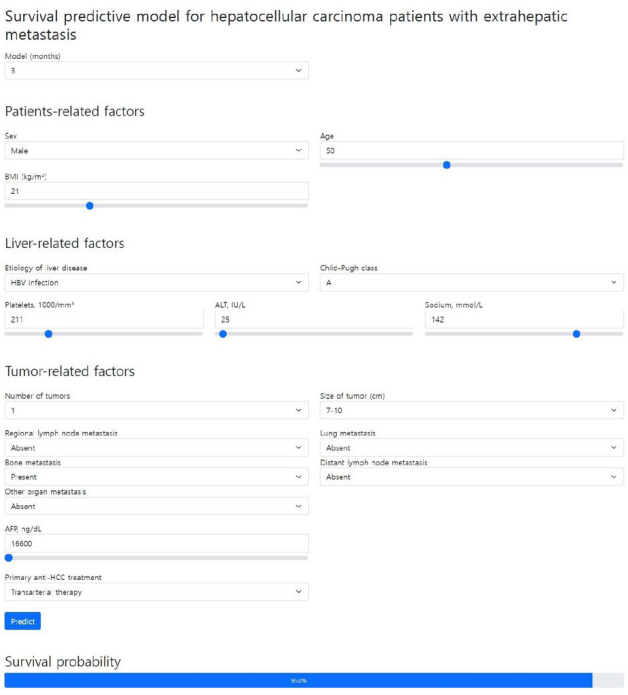
Aims: Accurate estimation of survival is of utmost importance in patients with hepatocellular carcinoma (HCC) and extrahepatic metastasis. This study aimed to develop a survival prediction model using real-world data.

Methods: A total of 993 patients with treatment-naïve HCC and extrahepatic metastasis were included from 13 Korean hospitals between 2013 and 2018. Patients were randomly divided into a training set (70.0%) and a test set (30.0%). The eXtreme Gradient Boosting (XGBoost) algorithm was applied to predict survival at 3, 6, and 12 months.

Results: The mean age of patients was 60.8±12.3 years, 85.4% were male. Of these patients, 96.1% died, and median survival duration was 4.0 months. In multivariate analysis, Child-Pugh class, number and size of tumors, presence of vascular or bile duct invasion, lung or bone metastasis, serum AFP, and primary anti-HCC treatment were associated with survival. We constructed model for survival prediction based on relevant variables, which is available online (https://metastatic-hcc.onrender.com/form). Our model demonstrated high performance with areas under the receiver operating characteristic curves of 0.778, 0.794, and 0.784 at 3, 6, and 12 months, respectively. Feature importance analysis indicated that primary anti-HCC treatment had the highest importance.

Conclusions: We developed a model to predict the survival of patients with HCC and extrahepatic metastasis, which demonstrated good discriminative ability. Our model would be helpful for personalized treatment and for improving the prognosis.

Keywords: Liver neoplasms, Prognosis, Survival rate, Probability



PE-135

Clinical Characteristics and Prognostic Factors of 80 Years or Older Patients with Hepatocellular Carcinoma

Hoon Gil Jo[1], Eun Young Cho[1], Jeong Mi Lee[2], Hye Jin Kang[3], Chang Hun Lee[3], In Hee Kim[3]

[1]Department of Internal Medicine, Wonkwang University School of Medicine and Hospital, [2]Department of Public Health, Wonkwang University Graduate School, [3]Department of Internal Medicine, Jeonbuk National University School of Medicine and Hospital

Aims: Although the prevalence of hepatocellular carcinoma (HCC) has recently decreased due to applying of vaccines and antiviral agents, the incidence of HCC in extremely elderly (>80 years) patients is increasing. However, it may be challenging to treat it actively due to many comorbidities, deterioration of physical function, and very old age. Therefore, we undertook to identify the clinical characteristics and prognostic factors of patients with HCC aged 80 years or more.

Methods: A total of 233 treatment-naïve extremely elderly patients with HCC who visited 2 tertiary university hospital in Jeonbuk province from January 2010 to December 2021 were enrolled. We retrospectively reviewed the patients' medical records including medical history and finding of laboratory, and imaging studies.

Results: A total 233 elderly patients were included, 40 were diagnosed in 2013 to 2015, 83 in 2016 to 2018, and 95 in 2019 to 2021. The proportion of patients diagnosed after 2015 is significantly high. The mean age of 83.3±3.07 years, 71.2% (166/233) were male and 60.9% (142/233) had liver cirrhosis at the time of diagnosis. The etiologic

diseases associated with the development of HCC were HBV (n=34, 14.6%), HCV (n=43, 18.5%), alcohol (n=48, 20.6%), and others (n=9, 3.9%), and unknown (n=99. 42.5%). At the time of diagnosis, the tumor stage was mUICC stage was 1, 37 (15.9%); 2, 86 (36.9%); 3, 63 (27.0%); 4, 47 (20.2%) and BCLC stage 0, 24 (10.3%); A, 62 (26.6%); B, 29 (12.4%); C, 67 (28.8%); D, 51 (21.9%). And, 49.4% (115/233) of patients received treatment after diagnosis of HCC, 50.6% (118/233) did not receive treatment. Patients with prolonged follow-up for more than 3 years were mainly patients who were actively treated (treated 22.6% and untreated 5.1%, p=0.000) and early-stage tumor patients (mUICC stage 1, 37.8%; 2, 15.1%; 3, 7.9%; and 4, 0%, p=0.000 and BCLC stage 0, 41.7%; A, 24.2%; B, 10.3%; C, 4.5% and D, 2.0%, p=0.000, respectively).

Conclusions: In extremely elderly patients, the risk factors of HCC were often ambiguous and diagnosed at a more advanced stage. Factors related to prognosis were tumor stage and whether or not treated. Therefore, even if elderly patient does not have well-known risk factors for HCC, it is necessary to check a regular health examination including abdominal ultrasonography if chronic liver disease was suspected.

Keywords: Hepatocellular carcinoma, Elderly patients, Treatment

PE-136

Recurrence of Hepatocellular Carcinoma in Non-Cirrhotic Patients with Non-Alcoholic Fatty Liver Disease versus Hepatitis B Infection

Jungnam Lee[1†], Jong-In Chang[2†], Young-Joo Jin[1*], Jeong-Hoon Lee[3*], Ju Yeon Kim[3], Dong Hyun Sinn[4], Soon Sun Kim[5], Hyun Woong Lee[6], Jung Hwan Yu[1], Jin-Woo Lee[1]

[1]Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, South Korea, [2]Department of Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, South Korea, [3]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea, [4]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [5]Department of Gastroenterology, Ajou University School of Medicine, Suwon, South Korea, [6]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Aims: We conducted this multi-center study to evaluate the long-term cumulative recurrence rates of HCC and OSs after curative resection for HCC in non-cirrhotic NAFLD patients. In addition, we compared these outcomes of non-cirrhotic NAFLD patients with those of HBV patients with or without fatty liver (FL).

Methods: We retrospectively analyzed data extracted from the records of 791 consecutive patients that underwent surgical resection (SR) as an initial treatment for initially diagnosed primary HCC at six university hospitals between January 2005 and December 2015.

Results: Recurrence of HCC was observed in 6 (9.5%) and 210 (28.8%) patients in the NAFLD and HBV groups, respectively, during median follow-ups of 69.9 and 85.2 months. Cumulative recurrence rates in the NAFLD group at 2, 4, 6, 8, and 10 years (3.6, 9.4, 12.4, 12.4, and 12.4%, respectively) were significantly lower than in the HBV group (1.7, 16.9, 27.2, 37.1, and 44.4%, respectively) (p=0.008). Cumulative overall survival (OS) rates in the NAFLD group at 2, 4, 6, 8, and 10 years (98.2, 96.0, 84.0, 84.0, and 84.0 %, respectively) were significantly lower than in the HBV group (99.3, 98.4, 97.3, 95.7, and 93.6%, respectively) (p=0.003). HBV infection, with or without fatty liver (FL) compared to NAFLD, were significant predictors for the recurrence of HCC (p<0.05 for all) and OS (p<0.05 for all), respectively.

Conclusions: Non-cirrhotic NAFLD patients showed lower recurrence rates of HCC but poorer survival outcomes than non-cirrhotic HBV patients with or without FL.. The recurrence risk of HCC remains even in non-cirrhotic NAFLD patients.

Keywords: Recurrence, HCC, NAFLD, HBV

PE-137

Growth Rate of Untreated HCC in Patients with over 80 Years of Age

Dong Yune Ahn[1], Hoon Gil Jo[1], Eun Young Cho[1], Jeong Mi Lee[2], Hye Jin Kang[3], Chang Hun Lee[3], In Hee Kim[3]

[1]Department of Internal Medicine, Wonkwang University School of Medicine and Hospital, [2]Department of Public Health, Wonkwang University Graduate School[2], Department of Internal Medicine, Jeonbuk National University School of Medicine and Hospital

Aims: Some studies have shown that the younger the age and the more advanced the hepatocellular carcinoma (HCC) stage at diagnosis, the faster HCC growth from tumor occurrence. This study aims at investigating about the tumor growth rate and the factors affecting it in patients with HCC who were not treated and who had only follow-up imaging studies among extremely elderly HCC patients aged 80 years or older.

Methods: From January 2010 to December 2021, 20 of the 233 elderly patients (aged 80 or older) who visited the gastroenterology department of two tertiary university hospitals and were diagnosed with HCC were enrolled who did not receive HCC treatment and who had follow-up imaging studies at least once after diagnosis. We retrospectively reviewed the patients' medical records, laboratory value, and imaging tests. The calculation formula of the total volume doubling time (TVDT) is as follows; TVDT=(T - T0) × log2 / (log TV/TV0), TV (total volume)=(4/3) × π × (D/2)^3, where D is the maximum diameter.

Results: 1. Of the total 233 patients, 118 patients (50.6%) did not receive HCC treatment, and 20 patients (16.9%) were follow-up imaging studies more than once after being diagnosed with HCC. The median follow-up period was 355 days (56-1036 days). 2. The median value of the total volume doubling time was 144 days (37 days to 996 days). 3. When comparing each parameter by dividing the two groups based on 144 days of TVDT (144 days or less=shorter[S] group, over 144 days=longer[L] group), all patients over 85 years of age were included in L group, and there were more patients without cirrhosis in group S (S=55.6% vs L=33.3%). There was a tendency to be included in the S group as tumor stage advanced (in the case of stage 3&4, S=66.6% vs. L=22.2%). 4. Among the serology values and the score using it, only the PIVKA value showed a significant difference (S=137.33 vs. L=15929.43, p=0.014).

Conclusions: The median TVDT of HCC in extremely elderly patients aged 80 years or older was 144 days, which tended to be longer than the previously reported TVDT of HCC (85 to 114 days) that did not consider age. high PIVKA value at diagnosis, less than 85 years, no cirrhosis, and advanced tumor stage showed relatively short

TVDT despite being too old. Therefore, it is necessary to recommend treatment if possible in case of these characteristics.

Keywords: Hepatocellular carcinoma, Aged, 80 and over, Growth rate

PE-138

Efficacy Comparison of First-Line Therapies of Unresectable Hepatocellular Carcinoma in Older Age Patients

Ahlim Lee[1,2], Ji Hoon Kim[2], Soon Kyu Lee[2], Ji Won Han[2], Hyun Yang[2,3*], Heechul Nam[2], Hae Lim Lee[2], Pil Soo Sung[2], Hee Yeon Kim[2], Jung Hyun Kwon[2], Jeong Won Jang[2], Si Hyun Bae[2,3], Jong Young Choi[2], Seung Kew Yoon[2]

[1]Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, [3]Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea

Aims: After the IMbrave150 trial, atezolizumab plus bevacizumab (AteBeva) became the first-line therapy for unresectable hepatocellular carcinoma (HCC). However, few studies compared efficacy in elderly patients older than 65 with lenvatinib or sorafenib, the other first-line therapies. This study compared the efficacy of first-line agents for unresectable HCC in patients over 65.

Methods: Between September 2020 to December 2022, 162 patients older than 65 from eight hospitals of Catholic Medical Center receiving AteBeva, lenvatinib, and sorafenib were included. We excluded the patients who received systemic treatment before this therapy. Overall survival (OS), time to progression (TTP), and progression-free survival (PFS) were measured in each treatment group of patients.

Results: In baseline characteristics, there were no significant differences among the three treatment groups in terms of median age, sex, etiology, Child-Pugh class, performance status of patients, and BCLC stage. At the time of analysis, 57 patients (35 %) had died. Survival rate was comparable between these treatment cohorts with AteBeva having a mean survival of 8.9 months compared to 11.0 months for those receiving lenvatinib, and 10.6 months for sorafenib (p=0.646). Mean TTP and PFS showed differences between these groups (TTP 6.7 vs. 10.7 vs. 5.3 months, respectively, p=0.014; PFS 5.8 vs. 7.8 vs. 4.5 months, p=0.055). In best response analysis, AteBeva and lenvatinib show superiority to sorafenib in terms of objective response rate (ORR) and disease control rate (DCR) with statistical significance (ORR 30.9 vs. 37.1 vs. 11.1%, respectively, p=0.032; DCR 72.7 vs. 71.4 vs. 44.4%, p=0.013).

Conclusions: In patients older than 65, there was no significant difference in the treatment efficacy of the three first-line therapies for unresectable HCC in terms of OS. However, in TTP, ORR, and DCR, AteBeva and lenvatinib show superiority to sorafenib, and in PFS, lenvatinib is superior to sorafenib with statistical significance. Therefore, if elderly patients cannot be received AteBeva due to any complication risks, lenvatinib are commendable alternative without concern for decreased therapeutic effect. Further studies are needed to compare the exact treatment response.

Keywords: Hepatocellular carcinoma, Atezolizumab/bevacizumab, Lenvatinib, Sorafenib, Older age

PE-139

Efficacy of Cabozantinib after Sorafenib Treatment for Advanced Hepatocellular Carcinoma

Ahlim Lee[1,2], Ji Hoon Kim[2], Soon Kyu Lee[2], Ji Won Han[2,3], Hyun Yang[2], Heechul Nam[2], Hae Lim Lee[2], Pil Soo Sung[2,3], Hee Yeon Kim[2], Jung Hyun Kwon[2], Jeong Won Jang[2,3*], Si Hyun Bae[2], Jong Young Choi[2,3], Seung Kew Yoon[2,3]

[1]Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, [3]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea

Aims: Cabozantinib is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptors, MET, and AXL. In phase 3 CELESTIAL trial, cabozantinib improved overall survival(OS) and progression-free survival(PFS) compared with the placebo group for the patients of the advanced stage of hepatocellular carcinoma(HCC) previously treated with sorafenib. This study verified the real-world efficacy of cabozantinib for HCC patients previously treated with sorafenib.

Methods: Between October 2019 to December 2022, 45 adult patients from eight hospitals of Catholic Medical Center were treated with cabozantinib for the advanced stage of HCC. All patients treated with one or more systemic chemotherapy regimens including sorafenib before cabozantinib but underwent disease progression were enrolled.

Results: The median age was 60(interquartile range, 54.5-65.0) years, and 35(77.8%) patients were male. The most common etiology of chronic liver disease was hepatitis B infection(73.3%). With a median follow-up duration of 5.0 months(IQR95% CI, 2.0-11.5), the median OS was 7.0 months(95% CI, 2.4-11.5), and the median time to progression(TTP) was 3.0 months(95% CI, 1.2-4.8), and the median PFS was 3.0 months(95% CI, 1.8-4.2). The objective response rate and the disease control rate were 11.1% and 48.9%, respectively. In multivariate analysis, variables associated with OS were Child-Pugh(CP) class, HR 10.33(CP class C to B, 95% CI; 2.88-37.03, p=0.000) and portal vein tumor thrombosis with the extrahepatic spread at treatment start, HR 2.337(yes to no, 95% CI; 0.99-5.53, p=0.053). The variable associated with TTP was albumin, HR 0.349(above the median to under, 95% CI 0.158-0.772, p=0.009).

Conclusions: This study showed a consistent efficacy outcome of cabozantinib with the phase 3 CELESTIAL trial and a Korean multicenter retrospective analysis. Further studies are needed to evaluate the exact treatment response and find the new role of cabozantinib after the failure of the new standard first-line treatment.

Keywords: Hepatocellular carcinoma, Cabozantinib, Sorafenib, Efficacy

PE-140

Machine Learning Model for Driver Gene Identification Reveals Roles of Interferon Stimulated Genes in Sorafenib Resistance of HCC

Deok Hwa Seo[1], Min woo Kang[1], Byung Yoon Kang[1], Ji woo Park[2], Hee won Jung[2], Seung Kew Yoon[3], Won hee Hur[4], Jae gyoon Ahn[2,*] Pil Soo Sung[1,3,*]

[1]The Catholic University Liver Research Center, College of Medicine, Depart-

ment of Biomedicine & Health Sciences, POSTECH-Catholic Biomedical Engineering Institute, The Catholic University of Korea, Seoul 06591, Republic of Korea, [2]Department of Computer Science and Engineering, Incheon National University, Incheon 22012, Republic of Korea, [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul 06591, Republic of Korea, [4]Division of Viral Disease Research, Center for Infectious Disease Research, Korea National Institute of Health, Chungbuk 28159, Republic of Korea

Aims: Sorafenib, a multi targeted tyrosine kinase inhibitor, is an approved as a therapeutic agent for hepatocellular carcinoma (HCC), however, patients still present disease progression. Unphosphorylated ISGF3 (U-ISGF3) is known to DNA damage resistance by the upregulation of a group of interferon stimulated genes (ISGs). In this study, we investigated the relationship between sorafenib resistance and ISGs in HCC cells.

Methods: Huh7, Hep3B and HepG2 human HCC cell lines were continuously exposed to sorafenib. U-ISGs and ISGs expression were examined by qRT-PCR. We identified cancer driver genes that are specifically present in samples resistant to sorafenib. To accomplish this, we utilized a machine learning model called MPD (IEEE Access, vol. 10, pp. 54245-54253, 2022) on gene expression and mutation data from Huh7, Hep3B, and HepG2 samples. MPD (Machine learning model for Patient-specific Driver gene identification) is designed to detect patterns revealing the impact of known driver genes on other genes within gene networks.

Results: We examined the expression of the U-ISGF3 components and U-ISGs in HCC cell lines with sorafenib resistance. Using immunoblotting, high level of IRF9 was observed in sorafenib resistance cell lines than in control cell lines, in all of the three hepatoma cell lines. Also. The expression of U-ISGs were increased in sorafenib resistance cells, including OAS1, BST2, MAP3K and IFI27. By contrast, ISGs regulated only by ISGF3, including MyD88, ADAR and PKR were not increased in sorafenib resistance cells in compared with mock treated cells.

Conclusions: These data show that continuous exposure of HCC cell lines to sorafenib upregulates IRF9, U-ISGs and increases cell survival.

Keywords: Sorafenib resistance, HCC, IRF9

PE-141

Long-Term Outcomes of Liver Transplantation for Patients with Hepatocellular Carcinoma beyond Milan Criteria: A Multicenter Cohort Study

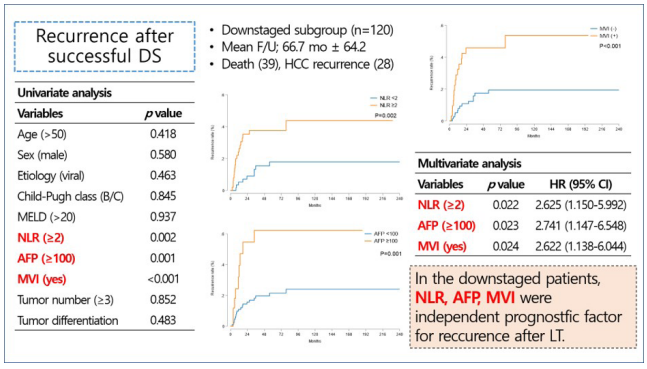
Heechul Nam[1,2], Pil Soo Sung[1,2], Hee Yeon Kim[1,2], Ho Joong Choi[3], Gun-Hyung Na[3], Jung Hyun Kwon[1,2], U Im Chang[1,2], Chang Wook Kim[1,2], Si Hyun Bae[1,2], Young Kyoung You[3], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jin Mo Yang[1,2], Jeong Won Jang[1,2*]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]The Catholic Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3]Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Recent guidelines recommend that liver transplantation (LT) can be considered for patients with hepatocellular carcinoma (HCC) that exceeds Milan criteria (MC) if they have been successfully downstaged to within MC. However, multi-center studies analyzing long-term outcomes are lacking. This study aims to identify prognostic factors for overall survival (OS) and recurrence after LT in downstaged patients with HCC beyond MC.

Methods: This is a multi-center retrospective study on consecutive patients with HCC underwent LT at 6 academic centers from September 1995 to September 2022. The associations of factors on OS and recurrence rate were analyzed using Cox proportional hazards regression and multivariable logistic regression models.

Results: The study included 614 HCC patients who underwent LT and were categorized into three groups: within MC (n=380), successfully down-staged (DS, n=120), and not down-staged (NoDS, n=114). The median age of the patients was 54 years (IQR, 50-60 years) and the majority of them were male (509 [82.9%]). The mean follow-up after LT was 77.1 months±67.8, corresponding to a total of 3904.6 person-years. During this follow-up period, there were 179 deaths and 104 cases of HCC recurrence. There were significant differences observed in OS based on MC and downstaging. The OS rates at 1, 3, 5, 10, and 20 years were 92.5%, 85.4%, 82.9%, 75.1%, and 63.3% for patients within MC; 89.8%, 74.8%, 68.1%, 59.5%, and 51.0% for DS; and 72.9%, 52.1%, 50.8%, 39.7%, and 36.9% for NoDS, respectively (p<0.001). Recurrence rates were also significantly better for the DS group compared to the NoDS group. The recurrence rates at 1, 3, 5, 10, and 20 years were 2.5%, 6.7%, 8.8%, 9.8%, and 9.8% for patients within MC; 13.9%, 25.6%, 27.1%, 29.3%, and 29.3% for DS; and 36.3%, 43.9%, 48.5%, 48.5%, and 56.3% for NoDS, respectively (p<0.001). In the DS group, independent prognostic factors associated with recurrence after LT were neutrophil-to-lymphocyte ratio (NLR) ≥2 at LT (HR, 2.625; 95% CI, 1.150-5.992; p=0.022), alpha-fetoprotein (AFP) ≥100 (HR, 2.741; 95% CI, 1.147-6.548; p=0.023), and microvascular invasion (MVI) on explant pathology (HR, 2.622; 95% CI, 1.138-6.044; p=0.024).



Conclusions: This multi-center retrospective cohort study with long-term follow-up demonstrated favorable outcomes in patients with HCC who achieved successful downstaging to meet MC before undergoing LT. Specifically, patients with NLR (<2), AFP (<100), and no MVI exhibited significantly lower recurrence rates and better post-LT outcomes. These findings suggest the importance of successful downstaging and highlight the potential prognostic value of NLR, AFP, and MVI in predicting outcomes after LT for HCC.

Keywords: Hepatocellular carcinoma, Liver transplantation, Downstaging treatment, Beyond milan criteria

PE-142

Impact of Prior TACE History on the Outcome of HCC Patients Undergoing TKI versus ICI: A Real-World Analysis

Kwon Yong Tak, Jeong Won Jang[1], Ji Hoon Kim[1], Ahlim Lee[2], Ji Won Han[1], Soon Kyu Lee[3], Hyun Yang[4], Hee Chul Nam[5], Pil Soo Sung[1], Hee Yeon Kim[5], Seok Hwan Kim[6], Hae Lim Lee[7], Myeong Jun Song[6], Jung Hyun Kwon[3], U Im Chang[2], Chang Wook Kim[5], Soon Woo Nam[3], Si Hyun Bae[4], Jong Young Choi[1], Seung Kew Yoon[1]

Graduate School of Medical Science and Engineering, Biomedical Research Center, Korea Advanced Institute of Science and Technology, Daejeon, Republic of Korea, [1]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [2]Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea, [3]Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [4]Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [5]Department of Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, Korea, [6]Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, South Korea, [7]Department of Internal Medicine, Bucheon St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, Korea

Aims: The appropriate timing for conversion to systemic therapy remains uncertain for hepatocellular carcinoma (HCC) patients with ineffective response to transarterial chemoembolization (TACE). This multicenter, real-world cohort study aimed to examine the impact of prior TACE history on the outcome of HCC patients undergoing immune checkpoint inhibitor (ICI) and tyrosine kinase inhibitor (TKI).

Methods: Between 2016 and 2022, HCC patients who received TKI (n=658) and ICI (n=230) treatments and met the eligibility criteria were recruited for the study. 521 (58.7%) patients underwent conversion from TACE to systemic therapies. Primary outcome was time-to-progression (PFS). The outcome measures were evaluated stratifying by prior TACE history and type of systemic therapy.

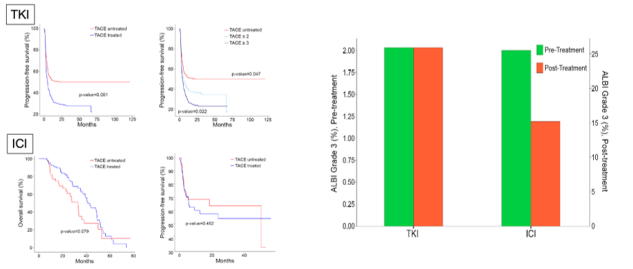
Results: The median follow-up period was 8.6 months. In multivariate analysis, prior TACE history was identified as an independent factor for poor OS (p=0.029) and PFS (p=0.048) in TKI-treated patients. PFS was significantly worse in TKI-treated patients with prior TACE history than those without (median 4.3 vs. 9.0 months, respectively; p<0.001). In particular, patients who had received three or more prior TACE procedures had significantly worse PFS than those who had received one or two prior TACE (5.3 vs 3.8 months, p=0.022). For the prior TACE-treated group, the development of hepatic impairment (ALBI grade 3) more frequently occurred during TKI than ICI therapy, with a 12.7-fold vs. 7.6-fold increase post-treatment, respectively (p<0.001). Unlike TKI-treated patients, prior TACE history did not have significant effects on OS (8.9 vs 9.7 months, p=0.079) or PFS (5.0 vs 3.9 months, p=0.452) for ICI-treated patients.

Conclusions: The impact of prior TACE history on the efficacy of subsequent systemic therapy for HCC may differ depending on the type of therapy. Multiple TACE procedures are more likely to adversely affect the outcome of subsequent TKI therapy, resulting in higher risk of developing hepatic impairment and eventually worse patient outcome.

Keywords: Hepatocellular carcinoma, ICI, TKI, Survival

Variable	Total (n=888) N (%) or median (ranges)
Age (yr)	62.7 (26-93)
Sex	
Male	735 (82.8%)
Etiology	
Hepatitis B	499 (56.2%)
Hepatitis C	58 (6.5%)
Alcohol	125 (14.1%)
Treatment	
TKI	658 (74.1%)
ICI	230 (25.9%)
AFP	
≤400	465 (52.4%)
ECOG	
0-1	858 (96.6%)
≥2	30 (3.4%)
Child-pugh score	
A	721 (81.2%)
ALBI grade	
1	241 (35.0%)
2	425 (61.8%)
3	22 (3.2%)
BCLC grade	
C	810 (91.3%)

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex: female	1.030 (0.838-1.268)	0.777	-	-
Age < 50	1.060 (0.838-1.340)	0.628	-	-
Child A	1.349 (1.109-1.639)	0.002	1.234 (1.013-1.512)	0.037
AFP ≤ 400	1.008 (0.861-1.180)	0.924	-	-
BCLC 0-2	1.056 (0.793-1.406)	0.709	-	-
ECOG 0-1	1.543 (1.016-2.342)	0.042	1.565 (1.048-2.339)	0.029
Combination therapy	0.915 (0.711-1.177)	0.490	-	-
TKI as first line	0.708 (0.571-0.878)	0.049	0.862 (0.676-1.099)	0.230
previous TACE	0.726 (0.620-0.851)	<0.001	0.813 (0.679-0.973)	0.024



PE-143

The Utility of PIVKA-II as a Biomarker for Treatment Response in Hepatocellular Carcinoma

Charmaine Patricia Varquez[1], Madalinee Eternity Labio[2]

Department of Medicine, Section of Gastroenterology, Makati Medical Center, Philippines

Aims: Progressive hepatocellular carcinoma remains difficult to cure despite significant advances in its treatment. Consequently, there is a growing need for biochemical markers which may potentially detect disease progression posttreatment, and guide decisions to switch therapy.

Methods: A single center, retrospective analytical cohort study was done at a tertiary hospital. Data was collected on Early, Intermediate or Advanced stage HCC patients who received: Ablation, transarterial chemoembolization, resection, tyrosine kinase inhibitors, or atezolizumab+bevacizumab. Baseline patient demographics including tumor characteristics on imaging were collected. Pre and post treatment Alpha Fetoprotein and PIVKA II levels were gathered. Comparisons of PIVKA-II and AFP across cohort characteristics were performed using Spearman&s (rho) correlation coefficients. Analyses were performed using IBM SPSS 22 with p<0.05 deemed to be indicative of statistical significance.

Results: Results show that there is concordance of PIVKA II levels with treatments responses by mRECIST criteria. A significant difference was seen between pre-treatment and post-treatment PIVKA II levels in patients who underwent resection and received tyrosine kinase inhibitors. A positive relationship between PIVKA-II with the size of the largest HCC lesion by imaging was depicted.
The mean age of participants was 68 years, predominantly male. Non-viral causes were found in the majority (67%). Most were classi-

fied as Child Pugh A (58%); BCLC B and C (36% and 31%) were the most frequent stage while A and D were the least frequent.

Conclusions: Based on current literature, PIVKA II shows promise as a more sensitive biomarker compared to AFP. Our study reveals an association of PIVKA II with tumor size and its concordance with treatment response by imaging criteria. Using AFP alone may not discriminate between pre and post treatment responses but the addition of PIVKA II or the use of PIVKA II alone may serve as a better predictor of response to treatment.

Keywords: PIVKA II, Utility, Treatment response, Hepatocellular carcinoma, Biomarker

	Pre-treatment	Post-treatment	P-Value
	PIVKA II		
Overall	531.8 (67.4, 9989.8)	471.3 (67.0, 2918.4)	0.2628
Ablation (Radiofrequency/ Microwave)	235.4 (43.7, 1476.2)	213.7 (68.9, 712.6)	0.6784
Atezolizumab + Bevacizumab	88856.6 (36.7, 177676.5)	21221.3 (30.2, 42412.4)	0.1797
Resection	140.8 (32.6, 1623.0)	48.8 (19.2, 930.3)	**0.0050**
Trans arterial Chemoembolization	7473.1 (4734.3, 345881.0)	2527.5 (165.1, 1989158.0)	0.8653
Tyrosine Kinase Inhibitors	2616.4 (330.5, 50979.8)	2031.7 (620.5, 56012.6)	**0.0464**
	AFP		
Overall	10.2 (3.9, 254.3)	9.1 (3.9, 103.7)	0.1312
Ablation (Radiofrequency/ Microwave)	8.5 (4.4, 10.6)	6.9 (3.7, 55.7)	0.0867
Atezolizumab + Bevacizumab	7103.5 (6.7, 14200.3)	6795.5 (6.8, 13584.2)	0.6547
Resection	8.3 (2.8, 251.0)	15.3 (5.3, 160.6)	0.0924
Trans arterial Chemoembolization	10.9 (4.0, 35.6)	4.1 (3.2, 74.3)	0.5937
Tyrosine Kinase Inhibitors	83.3 (5.1, 1225.5)	29.2 (4.2, 1328.5)	0.0747

Change in	Stable Disease	Progressive Disease	Partial Response	Complete Response	P-value
PIVKA II					
Increase	3 (25.0)	5 (41.7)	1 (8.3)	3 (25.0)	0.003
Decrease	3 (13.6)	0 (0.0)	8 (36.4)	11 (50.0)	
AFP					
Increase	5 (31.2)	5 (31.2)	1 (6.2)	5 (31.2)	0.052
Decrease	4 (16.7)	2 (8.3)	9 (37.5)	9 (37.5)	

PE-144

Utilization of Community-Based Health Centers (Puskesmas) to Improve Accessibility of Health Services for Liver Patients

Rosinta Hotmaida Pebrianti Purba[1], Helen Try Juniasti[2]

[1]Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia, [2]Department of Public Health, Cendrawasih University, Papua, Indonesia

Aims: More than 10% or 28 million of Indonesia's population are liver patients. Liver disease is the fifth most prominent cause of death for the elderly in Indonesia and is 3.3 times more likely to cause death due to infection with the Sars-Cov2 virus. The burden of government social insurance financing for liver disease in 2018 was one of the highest or reaching $235 million. Because the progression of fatty liver is very gradual (the silent killer) and new cases are known after an advanced stage. The Ministry of Health carries out a preventive program that reaches remote areas through various screenings. Utilizing Community-Based Health Centers *(Puskesmas)* as health facility that provides sub-district-based integrated services is expected to be early detection of liver disease. However, little is known about the effectiveness of *Puskesmas* in the framework of controlling liver disease.

Methods: We utilize a longitudinal survey dataset from the 2014 Indonesia Family Life Survey (IFLS) to analyze and evaluate the effectiveness of the *Puskesmas* in improving the function of early liver disease detection. IFLS is a multi-level (individual, household, community, and facility levels), multi-topic, large-scale, and longitudinal survey that has been conducted in five waves since 1993. IFLS 2014 covers only 24 of all 34 Indonesian provinces. However, the covered provinces are also the most populated ones, so the survey is representative of 83% of the Indonesian population.

Results: The analysis shows that the liver disease prevalence among observations is 1,9%. However, the percentage increases in senior citizens by two times or 3,8%, and 60% are men. The elderly with liver disease, whether they have government social insurance or not, tend to access treatment at the *Puskesmas*. Given that Indonesia uses the Gate-Keeper system, the first-level health facilities are at the sub-district or community level. In addition to this, *Posyandu Lansia*, as an extension of *Puskesmas*, is also utilized by older people for routine health checks, obtaining food/supplements, and various meetings and counseling from 80,353 *Posyandu Lansia* that spread across 81,616 villages in Indonesia. The *Posyandu Lansia* is also a space for the elderly to access savings and loan financial services, religious activities, and political activities. Community-based health care is highly effective in improving the senior QoL in various aspects of life. However, 56% of older people who do not have insurance prefer traditional practitioners.

Conclusions: The community-based health care outreach program is carried out by trained cadres whom the Ministry of Health jointly recruited, the Ministry of Social Affairs, and the Family Planning Agency. The *Posyandu Lansia* can be a forum that carries out early detection of liver disease and is very accessible in preventive programs and improving the elderly QoL through various health activities, hobbies, counseling, economics, religion, and politics. It also needs to address the covered social insurance for treatment and caregivers.

Keywords: Integrated care system, Liver early detection, Elderly with liver disease, Ageing market

PE-145

Aging in Place for Elderly Undergo Liver Transplantation: How Informal Care Could Help Maintaining Higher Quality of Life?

Ester Marnita Purba[1], Rosinta H P Purba[2], Helen Try Juniasti[3], Lintong H Simbolon[4]

[1]Department of Industrial Engineering, Widyamataram University, Yogyakarta, Indonesia, [2]Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia, [3]Department of Public Health, Cendrawasih university, Papua, Indonesia, [4]Department of Law, University of Lampung, Lampung, Indonesia

Aims: The elderly (aged 60+ years) are the most vulnerable group to pancreatic cancer due to frequent comorbidities and mortality globally. Potential curative treatment is Liver Transplantation (LT), although long-term survival is less than satisfactory. Indonesia is entering an aging society while the Elderly with independence barriers reached 3.7% (Basic Health Research, MoH (2018)). The elderly post-LT is very dependent on the caregivers' existence to maintain their QoL. However, certified informal caregivers are not available in Indonesia, yet.

Methods: This study uses the 5th wave of the 2014 Indonesia Family Life Survey (IFLS), longitudinal and large-scale data to explore how the availability of caregivers in maintaining the Elderly QoL post-LT with Dementia comorbidity.

Results: Indonesian elderly reach 10.8% of the total population and 48% of them have chronic diseases. 18.6% of Liver cancer patients recorded in Indonesia are at Elderly age. As many as 23.7% of the elderly with post-LT were identified as having symptoms of dementia with moderate to severe severity which were assessed using the mini-cognitive test scoring. The elderly needing long-term care due to these health conditions reaches 9.7% and 88% of them do not have caregivers or take care of themselves. Only less than 1% of the elderly are cared for by paid caregivers and are concentrated in urban areas. The majority of the elderly are cared for by their families or tend to age in place or community. 36% of Elderly post-LT with dementia are holders of social protection programs so they benefit from health insurance and government social assistance. Using the Geriatric Depression Scale (GDS) it is known that the percentage of Elderly post-LT with dementia who has caregivers with mental health problems is lower than respondents who do not have caregivers.

Conclusions: As a country that will become the second-largest Silver Economy in the world after China, Indonesia is urgent to meet the availability of certified informal caregivers with standardization modules and training. Furthermore, expanding the coverage of health insurance for the provision of caregivers is a top priority because it mitigates mental health problems.

Keywords: Elderly post liver transplantation, Dementia status, Caregiver, Aging in community

PE-146

Multidimensional Quality of Life after Pediatric Liver Transplantation: Luck or Measurable Achievement?

Ester Marnita Purba[1], Rosinta H P Purba[2], Helen Try Juniasti[3], Hepri Ardianson Purba[4]

[1]Department of Industrial Engineering, Widyamataram University, Yogyakarta, Indonesia, [2]Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia, [3]Department of Public Health, Cendrawasih University, Papua, Indonesia, [4]Department of Economics, University of Lampung, Lampung, Indonesia

Aims: The field of pediatric liver transplantation (LT) has come a long way over the last 50 years. As short-term outcomes are excellent, the long-term effects of pediatric LT and its consequences on various aspects of quality of life have not been extensively examined. This is especially true for children who receive an LT while they are young, as infantile-onset liver disease, surgery, and immunosuppression can all have a negative impact on growth and neurodevelopment. The objective of this study was to use a validated measure for children to identify the status of physical health, mental well-being, and socioeconomic status in this cohort.

Methods: A systemic review of the English literature was carried out from an electronic database, covering all papers addressing long-term outcomes in pediatric liver transplants from 2000 to 2021.

Results: A physical summary score of the LT recipients was lower than the normal population, only 26% of our cohort achieved a composite outcome of 'meaningful survival'. Late outcomes after pediatric liver transplant affects the liver graft in the form of chronic liver dysfunction, humoral rejection, de novo autoimmune hepatitis, recurrent disease, metabolic syndrome, kidney dysfunction, and malignancy, worsened neurocognitive development, and shortages in allografts because of the cumulative exposure to the adverse effects of long-term immunosuppressive medications. The prevalence of common mental health problems is significantly higher than in the general population (26%): distress to fatigue, sleep difficulties, financial concerns, problems at work/school, worry, and low self-esteem. It worsened because the parents experienced more emotional stress and disruption of family activities. Sexual dysfunction only short-term impact post-transplant (3 months), but no long-term effect was found.

Conclusions: Importantly, despite normal liver function, many patients did not demonstrate 'meaningful survival'. We must refocus our efforts toward better understanding the long-term outcomes of children's "meaningful survival". The importance of promoting psychosocial support and family-centered care as key contributors to delivering a model towards the overarching goal of optimizing durable outcomes.

Keywords: Pediatric liver transplantation, Long-term effects, Meaningful survival, Family-centerd care

PE-147

Outcomes between Surgical Resection and Transarterial Chemoembolization in Patients with Multifocal BCLC-A and Child-Pugh B

Jiwon Yang, Won-Mook Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Jonggi Choi

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Aims: 2022 version of the Barcelona Clinic Liver Cancer (BCLC) system does not recommend resection for multinodular hepatocellular carcinoma (HCC) within Milan criteria. Thus, transarterial chemoembolization (TACE) is regarded the preferred treatment option. In addition, no specific recommendation exists regarding patients with Child-Pugh (CP) class B and this multifocal BCLC stage A of HCC. Therefore, we aimed to compare the outcomes between surgical resection and TACE in patients with multinodular HCC and CP class B.

Methods: We retrospectively analyzed 487 patients with multinodular treatment-naïve HCC within Milan criteria and CP class B who received either resection or TACE as an initial therapy at Asan Medical Center, Seoul, the Republic of Korea between 2013 and 2022. Overall survival (OS) was estimated using Kaplan-Meier method and comparison of the OS between resection and TACE was conducted by log-rank test. Propensity-score (PS) matching analysis was also used to minimize biases between the two groups. Cox proportional model was used to identify factors associated with a worse prognosis. Median follow-up period was 5.3 years.

Results: The median age was 68 years, and 85.0% of the patients were men. 72.5% of the patients had two lesions of HCC and the median size of the largest tumor was 2.0 cm. Median OS was significantly longer in the resection group than the TACE group (p<0.01). In

multivariate analysis, TACE (hazard ratio [HR]:1.91, 95% confidence intervals [CIs]:1.12-3.26, p=0.02), age (HR:1.05, 95% CIs:1.03-1.07, p<0.01), and tumor size (HR:1.41, 95% CIs:1.08-1.83, p=0.01) were associated with a worse prognosis. PS matched analysis also demonstrated that the resection group had a significantly longer OS than the TACE group (p=0.036).

Conclusions: In the present study, surgical resection showed a better OS than TACE in patients with multinodular HCC (within Milan criteria) and CP class B. Surgical resection can be considered as an effective treatment option in this category of patients.

Keywords: Barcelona clinic liver cancer, Chemoembolization, Surgical resection, Child pugh B, Hepatocellular carcinoma

PE-148

Comparison of Clinical Outcome between Nivolumab and Regorafenib as Second-Line Systemic Therapies after Sorafenib Failure in Patients with Advanced Hepatocellular Carcinoma

Hong Jun Lee[1*], Jae Seung Lee[2,3,4*], Ja Kyung Yoon[5], Jin-Young Choi[5], Hye Won Lee[2,3,4], Beom Kyung Kim[2,3,4], Seung Up Kim[2,3,4], Jun Yong Park[2,3,4], Sang Hoon Ahn[2,3,4], Do Young Kim[2,3,4]

[1]Yonsei University College of Medicine, Seoul 03722, Republic of Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul 03722, Republic of Korea; [3]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul 03722, Republic of Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul 03722, Republic of Korea; [5]Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul 03722, Republic of Korea

Aims: Nivolumab and regorafenib are second-line therapies for patients with advanced hepatocellular carcinoma (HCC). We aimed to compare the effectiveness of nivolumab to regorafenib.

Methods: We retrospectively reviewed HCC patients treated with nivolumab or regorafenib after sorafenib failure. Progression-free survival (PFS) and overall survival (OS) were analyzed. Inverse probability of treatment weighting (IPTW) using the propensity score (PS) was conducted to reduce treatment selection bias.

Results: Of the recruited 189 patients, 137 and 52 received regorafenib and nivolumab after sorafenib failure, respectively. Nivolumab users showed higher Child-Pugh B patients (42.3% vs. 24.1%) and shorter median sorafenib maintenance (2.2 vs. 3.5 months) than regorafenib users. Compared to regorafenib users, nivolumab users showed shorter median OS (4.2 vs. 7.4 months, p=0.045) and similar median PFS (1.8 vs. 2.7 months, p=0.070), respectively. However, median OS and PFS were not different between the two treatment groups after 1:1 PS matching yielded 34 pairs (log-rank p=0.810 and 0.810, respectively), and after stabilized IPTW (log-rank p=0.445 and 0.878, respectively). In addition, covariate-adjusted Cox regression analyses showed that the nivolumab (vs. regorafenib) use was not significantly associated with the PFS and OS after 1:1 PS matching and stabilized IPTW (all p>0.05).

Conclusions: Clinical outcomes in patients treated with nivolumab and regorafenib after sorafenib failure did not differ significantly.

Keywords: Hepatocellular carcinoma, Regorafenib, Nivolumab, Second-line therapy

PE-149

Statin on the Recurrence of Hepatocellular Carcinoma after Liver Transplantation: An Illusion Revealed by Exposure Density Sampling

Deok-Gie Kim[1], Eun-Ki Min[1], Seung Hyuk Yim[1], Mun Chae Choi[1], Hwa-Hee Koh[1], Minyu Kang[1], Jae Geun Lee[1], Myoung Soo Kim[1], Dong Jin Joo[1]

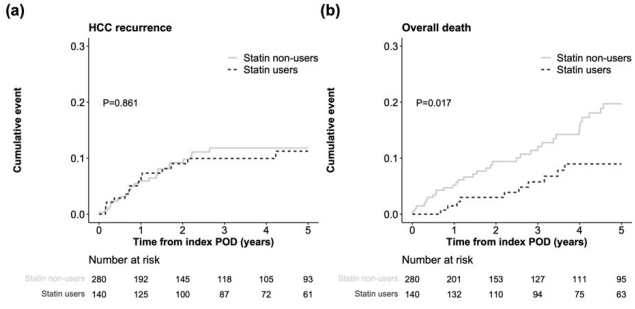
Department of Surgery, The Research Institute for Transplantation, Yonsei University College of Medicine, Seoul, South Korea

Aims: Benefit of statin has been reported to reduce not only overall death but also recurrence of hepatocellular carcinoma (HCC) in liver transplantation (LT) recipients. However, there was significant flaws regarding immortal time bias in previous retrospective studies.

Methods: From data of 658 patients who received LT for HCC, we matched 140 statin users to statin non-users with 1:2 manner at the time of first statin administration after LT using exposure density sampling (EDS) method. Propensity score calculated with baseline variables including explant pathology was used for EDS to equilibrate both groups. HCC recurrence and overall death were compared adjusting information at sampling time.

Results: Among statin users, median time for the statin start day was 219 (IQR 98-570) days, which was mainly moderate intensity (87.1%). Statin users and non-user controls sampled with EDS showed well-balanced baseline characteristics including detailed tumor pathology. Statin users and non-users showed similar HCC recurrence with cumulative incidence of 11.3% vs. 11.8% at 5 years, respectively (p=0.861). In multivariable Cox models (HR 1.04, p=0.918) and subgroup analysis, statin has no effect on HCC recurrence. In contrast, statin users showed significantly lower risk of overall death versus statin non-users (HR 0.28, p<0.001). There was no difference in type and intensity of statin between statin users who experienced HCC recurrence and those who did not.

Conclusions: When immortal time bias was controlled by EDS, statin showed no effect on HCC recurrence but still reduced mortality after LT. Statin use is encouraged for survival benefit but not for prevent HCC recurrence in LT recipients.



Keywords: Hepatocellcular carcinoma, Liver transplantation, Statin

PE-150

Acute Kidney Injury Predicts Poor Prognosis in Hepatocellular Carcinoma Patients with Spontaneous Bacterial Peritonitis

Min-Kyoung Kim[1], Ju-Yeon Cho[1,2]

[1]Department of Internal Medicine, Chosun University Hospital, [2]Department of Internal Medicine, Chosun University, College of Medicine

Aims: Spontaneous bacterial peritonitis (SBP) is an ominous complication of decompensated cirrhosis. This study aimed to assess the characteristics of hepatocellular carcinoma (HCC) patients who developed SBP and determine the factors associated with greater mortality.

Methods: A total of 36 HCC patients with a first episode of SBP between 2007 and 2016 were analyzed. Various clinical parameters including tumor stage and related risk factors of SBP including the ICA-AKI criteria were reviewed

Results: All patients were at BCLC stage C when diagnosed with HCC and the median time to the development of SBP 773 days. Portal vein invasion was present in 8 patients (22.2%) and extrahepatic metastasis was noted in 4 patients (11.1%). The Child-Pugh class at the diagnosis of SBP was B in 15 patients (41.7%) and C in 21 patients (58.3%). The ICA-AKI stage at the diagnosis of SBP was stage 0 in 18 (50%), stage 1 in 9 (25%), stage 2 in 7 (19%), and stage 3 in 2 patients (5.6%). Stage progression within 48 h after SBP diagnosis was noted in 3 patients (8.3%). Hyponatremia (serum sodium ≤130 mmol/L) and the diagnosis of type 1 hepatorenal syndrome according to the ICA-AKI criteria were factors associated with greater mortality.

Conclusions: Acute kidney injury and its progression are significant risk factors for mortality in HCC patients with SBP. The application of the ICA-AKI criteria is important for the early detection and intervention for a better prognosis in HCC patients with SBP.

Keywords: Hepatocellular carcinoma, Spontaneous bacterial peritonitis, Acute kidney injury

PE-151

Prognostic Value of Serum Alpha-Fetoprotein Level for Patients Undergoing Hepatectomy for Early-Stage (BCLC Stage 0/A) Hepatocellular Carcinoma: A Large Multicenter Analysis

Lan-Qing Yao[1], Zhong-Qi Fan[2], Ming-Da Wang[1], Ting-Hao Chen[3], Yong-Yi Zeng[4], Zhong Chen[5], Xian-Ming Wang[6], Ya-Hao Zhou[7], Jie Li[8], Xin-Ping Fan[9], Ying-Jian Liang[10], Feng Shen[1,11], Guo-Yue Lv[2*], Tian Yang[1,2,11*]

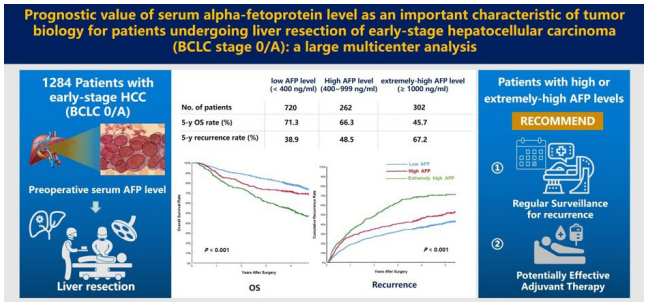
[1]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China, [2]Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, First Hospital of Jilin University, Changchun, Jilin, China, [3]Department of General Surgery, Ziyang First People's Hospital, Ziyang, Sichuan, China, [4]Department of Hepatobiliary Surgery, Mengchao Hepatobiliary Hospital, Fujian Medical University, Fujian, China, [5]Department of Hepatobiliary Surgery, Affiliated Hospital of Nantong University, Nantong, Jiangsu, China, [6]Department of General Surgery, First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, Shandong, China, [7]Department of Hepatobiliary Surgery, Pu'er People's Hospital, Pu'er, Yunnan, China, [8]Department of Hepatobiliary Surgery, Fuyang People's Hospital, Fuyang, Anhui, China, [9]Department of General Surgery, Pingxiang Mining Group General Hospital, Jiangxi, China, [10]Department of Hepatobiliary Surgery, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China, [11]Eastern Hepatobiliary Clinical Research Institute, Third Affiliated Hospital of Navy Medical University, Shanghai, China

Aims: According to the Barcelona Clinic Liver Cancer (BCLC) algorithm, tumor burden and liver function, but not tumor biology, are the key factors in determining tumor staging, treatment modality and evaluating treatment prognosis. Serum alpha-fetoprotein (AFP) level is an important characteristic of HCC biology, and we aimed to evaluate its prognostic value for patients undergoing liver resection of early-stage HCC (BCLC stage 0/A).

Methods: Patients who underwent curative liver resection for early-stage HCC between 2010 and 2019 were identified from a multi-institutional database. According to preoperative AFP levels, they were divided into three groups: the low (<400 ng/ml), high (400~999 ng/ml), and extremely-high AFP (≥1000 ng/ml) groups. Overall survival (OS) and recurrence rates were compared among these three groups.

Results: Among 1,284 patients, 720(56.1%), 262(20.4%), and 302 (23.5%) patients had preoperative low, high, and extremely-high AFP levels, respectively. The cumulative 5-year OS and recurrence rates were 71.3% and 38.9% among patients in the low AFP group, 66.3% and 48.5% in the high AFP group, and 45.7% and 67.2% in the extremely-high AFP group, respectively (both p<0.001). Multivariate Cox-regression analysis identified both high and extremely-high AFP levels to be independent risks of OS (hazard ratio: 1.275 and 1.978; 95% CI 1.004-1.620 and 1.588-2.464; p=0.047 and <0.001) and recurrence (1.290 and 2.050; 1.047-1.588 and 1.692-2.484; p=0.017 and <0.001).

Conclusions: This study demonstrates the important prognostic value of preoperative AFP level among patients undergoing resection for early-stage HCC. Incorporating AFP to prognostic estimation of the BCLC algorithm can help guide individualized risk stratification, identify neoadjuvant/adjuvant treatment necessity, and improve outcomes for early-stage HCC patients.



Keywords: Hepatocellular carcinoma, Alpha-fetoprotein, Recurrence, Survival, Barcelona clinic liver cancer

PE-152

Preoperative and Postoperative Variables for Rredicting Extrahepatic Metastasis of Hepatocellular Carcinoma after Curative Surgical Resection

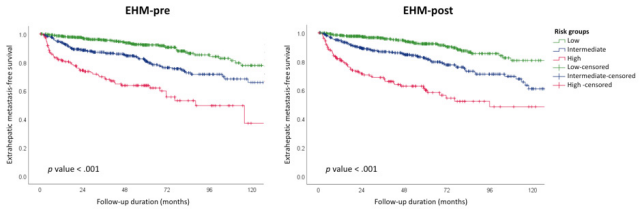
In Gun Yeo[1], Chang Hun Lee[1], Jae Hyun Yoon[2], Hoon Gil Jo[3], Eun Young Cho[3], Chung Hwan Jun[4], In Hee Kim[1]

[1]Department of Internal Medicine, Jeonbuk National University Medical School and Research Institute of Clinical Medicine of Jeonbuk National University Hospital-Jeonbuk National University Medical School, Korea, [2]Division of Gastroenterology, Department of Internal Medicine, Chonnam National University Medical School, Korea, [3]Department of Internal Medicine, Wonkwang University College of Medicine, Korea, [4]Department of Internal Medicine, Mokpo Hankook Hospital, Korea

Aims: Factors associated with extrahepatic metastasis (EHM) after curative treatment of hepatocellular carcinoma (HCC) have rarely been investigated. This study aimed to assess EHM occurrence after curative resection in HCC patients.

Methods: A retrospective review was conducted on treatment-naïve HCC patients who underwent curative resection between 2004 and 2019 at four tertiary hospitals. Recurrence characteristics after resection were evaluated, and predictors associated with EHM in HCC patients after curative resection were analyzed.

Results: A total of 1,069 HCC patients treated with surgical resection were enrolled for the study. The mean age was 59.1±10.2 years, with 85.8% of patients being male. The majority of patients (98.6%) had compensated liver cirrhosis, with chronic hepatitis B being the most common etiology of chronic liver disease (73.7%). During the follow-up period, there were 165 (19.6%) cases of EHM. Patients with EHM were younger and had a higher proportion of advanced modified UICC and BCLC stages, as well as a higher proportion beyond Milan criteria. Histologically, patients with EHM had larger tumor size and number, advanced Edmondson-Steiner (ES) grade, and a higher proportion of microvascular invasion, bile duct invasion, intrahepatic metastasis, and necrosis. Multivariate Cox regression analysis revealed that ln(Age), modified UICC stage, beyond Milan criteria, and ALBI grade ≥ 2 were independently significant factors associated with EHM in preoperative variables. Similarly, ln(Age), microvascular invasion, necrosis, beyond Milan criteria, and ALBI grade ≥ 2 were independently significant factors associated with EHM in postoperative variables. Kaplan-Meier plots clearly differentiated EHM-free survival among low, intermediate, and high-risk groups stratified by the EHM-preop and EHM-postop models.



Conclusions: This study analyzed preoperative and postoperative variables to predict EHM following curative surgical resection, resulting in the development of statistical models (EHM-preop and EHM-postop). These models have the potential to aid in clinical decision-making, but further validation studies are necessary.

Keywords: Carcinoma, Hepatocellular, Resection, Extrahepatic metastasis

PE-153

Efficacy of Renshenguben Oral Solution for Cancer-Related Fatigue among Patients with Advanced-Stage Hepatocellular Carcinoma: A Prospective Multicenter Cohort Study

Ming-Da Wang[1,2#], Chen Yuan[3#], Ke-Chun Wang[2#], Nan-Ya Wang[1#], Gao-Qi Ye[4], Ying-Jian Liang[5], Ya-Hao Zhou[6], Ting-Hao Chen[7], Jie Li[8], Zhi-Gang Chen[9], Hong Zhu[10], Xiang-Min Tong[3,11*], Tian Yang[1,2*]

[1]Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, First Hospital of Jilin University, Changchun, Jilin, China, [2]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China, [3]Department of Clinical Laboratory, Laboratory Medicine Center, Zhejiang Provincial People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China, [4]The Second School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China, [5]Department of Hepatobiliary Surgery, First Affiliated Hospital of Harbin Medical University, Heilongjiang, China, [6]Department of Hepatobiliary Surgery, Pu'er People's Hospital, Yunnan, China, [7]Department of General Surgery, Ziyang First People's Hospital, Sichuan, China, [8]Department of Hepatobiliary Surgery, Fuyang People's Hospital, Anhui, China, [9]Department of Hepatobiliary Surgery, Huaibei People's Hospital, Anhui, China, [10]Department of Medical Oncology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China, [11]Department of Central Laboratory, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

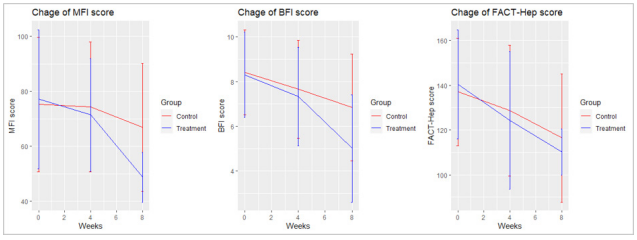
Aims: Cancer-related fatigue (CRF) is a common and debilitating symptom experienced by patients with advanced-stage cancer, especially those undergoing antitumor therapy. This study aimed to evaluate the efficacy and safety of Renshenguben (RSGB) oral solution, a ginseng-based traditional Chinese medicine, in alleviating CRF in patients with advanced hepatocellular carcinoma (HCC) receiving antitumor treatment.

Methods: Overall survival (OS) and recurrence rates were compared among these three groups. In this prospective, open-label, controlled, multicenter study, patients with advanced HCC at BCLC stage C and a Brief Fatigue Inventory (BFI) score of ≥4 were enrolled. Participants were assigned to the treatment group receiving RSGB (10 mL twice daily) or the control group receiving supportive care. Primary endpoint was the change in Multidimensional Fatigue Inventory (MFI) score at 4 and 8 weeks after enrollment. Secondary endpoints included changes in BFI and Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) scores at the same time points. Adverse events (AEs) and toxicities were assessed.

Results: A total of 409 participants were enrolled, with 206 assigned to the treatment group. Baseline clinical characteristics were comparable between groups (all P>0.05). At week 8, the treatment group exhibited a significant reduction in MFI score (p<0.05) compared to the control, indicating improved fatigue levels. Additionally, the treatment group showed significantly greater improvements in BFI and FACT-Hep scores at week 8 (p<0.05). At week 4, there was a trend towards improvement, but the differences were not statistically significant. Subgroup analyses among patients receiving various antitu-

mor treatments showed similar results. Multivariate linear regression analyses revealed that the treatment group experienced a significantly substantial improvement in changes of MFI, BFI, and FACT-Hep scores at week 8. No serious drug-related AEs or toxicities were observed.

Conclusions: RSGB oral solution effectively reduced CRF in patients with advanced HCC undergoing antitumor therapy over an eight-week period, with no discernible toxicities. These findings support the potential of RSGB oral solution as an adjunctive treatment for managing CRF in this patient population, warranting further investigation in larger, randomized controlled trials.



Keywords: Hepatocellular carcinoma, Cancer-related fatigue, Recurrence, Survival

PE-154

Efficacy and Feasibility of Perioperative Radiotherapy for HCC: A Quality-Based Systematic Review and Meta-Analyses

Chai Hong Rim[1,2*], Sunmin Park[1*], Won Sup Yoon[1,2]

[1]Department of Radiation Oncology, Ansan Hospital, Korea University Medical College, Ansan, Gyeonggi-do, Republic of Korea, [2]Department of Radiation Oncology, Korea University Medical College, Seoul, Korea

Aims: Although surgical resection has been the standard curative modality for hepatocellular carcinoma (HCC), more than two-thirds experiences intrahepatic recurrences. Given no standard perioperative treatment has been established, we performed a meta-analysis to evaluate the benefit of perioperative radiotherapy (RT).

Methods: The PubMed, Medline, EMBASE, and Cochrane Library were searched for studies published until May, 2023. Clinical studies, of which were randomized studies or propensity matched studies evaluating at least five major clinical factors (liver function [Child-Pugh criteria], tumor size, multiplicity, vessel invasion, and AFP level), comparing perioperative RT and surgery comparing surgery alone were included. The main effect measure is pooled odds ratios (OR) regarding benefit of perioperative radiotherapy, using 2-year overall survival (OS) and 1-year disease-free survival (DFS) data. Pooled percentile of temporal OS and PFS, and complication of grade ≥3 were also evaluated.

Results: Seven studies (5 randomized and 2 propensity-matched studies) involving 815 patients were included. In pooled analyses, pooled ORs regarding 1-year DFS and 2-year OS were 0.359 (95% confidence interval [CI]: 0.246-0.523) and 0.371 (95% CI: 0.293-0.576), in favor of perioperative radiotherapy, with very low heterogeneity. In subgroup analyses, benefit regarding OS and DFS were consistent in two subgroups (portal vein thrombosis [PVT] and narrow margin groups). In PVT subgroup, pooled OS rates for both 1 and 2 years (75.6% vs. 36.9%, p<0.001; 25.6% vs. 9.9%, p=0.004), DFS rates for both 1 and 2 years (25.2% vs. 10.3%, p=0.194; 11.9% vs. 3.0%, p=0.022) were higher with perioperative RT. In the narrow margin subgroup, surgery and radiotherapy group showed higher pooled OS rates for both 1 and 2 years (97.3% vs. 91.9%, p=0.042; 90.4% vs. 78.7%, p=0.051) and DFS (88.1% vs. 72.6%, p<0.001; 70.1% vs. 51.7%, p<0.001). Grade 5 toxicity was not reported, grade 4 toxicity occurred in one case, three studies reported grade ≥3 or higher LFT abnormality ranged from 4.8 to 19.2%, the most commonly reported type of toxicity.

Conclusions: The present study support oncologic benefit of perioperative RT. Selective analysis including high-quality comparative series and randomized studies provide reliable evidence. Although the prognoses of subgroup were different among subgroups, benefit of peroperative RT was valid in both subgroups.

Keywords: Hepatocellular carcinoma, Surgery, Radiotherapy, Survival

PE-155

Effects of Main Portal Vein Tumor Thrombi (PVTT) and Previous Locoregional Therapy (TACE) in Advanced Hepatocellular Carcinoma Treated with Lenvatinib

Suk-Pyo Shin[1], Jaekyung Cheon[1], Jooho Lee[1*], Hong Jae Chon[2], Young-Eun Chon[1], Yeonjung Ha[1], Kwan Sik Lee[1]

[1]Departments of Gastroenterology and Hepatology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, [2]Departments of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea

Aims: Lenvatinib has demonstrated its efficacy and safety in advanced hepatocellular carcinoma (HCC) in the phase III REFLECT clinical trial. It is important to note that patients with a huge tumor burden (i.e., the tumor occupies ≥50% of the liver) and main portal vein invasion, and poor liver function were not included in the REFLECT trial. We aimed to investigate the effects main PVTT and transarterial chemoembolization (TACE) before lenvatinib therapy for HCC patients in a real-world practice.

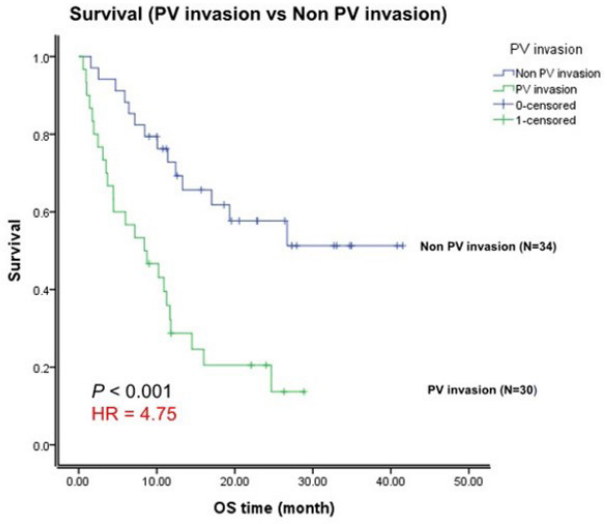
Methods: A retrospective study was conducted on 64 consecutive Korean patients who were treated with lenvatinib at CHA Bundang Hospital from February 2019 to August 2022. Tumor response was assessed according to mRECIST. We analyzed progression-free survival (PFS) and overall survival (OS) in relation to the baseline patients and tumor characteristics.

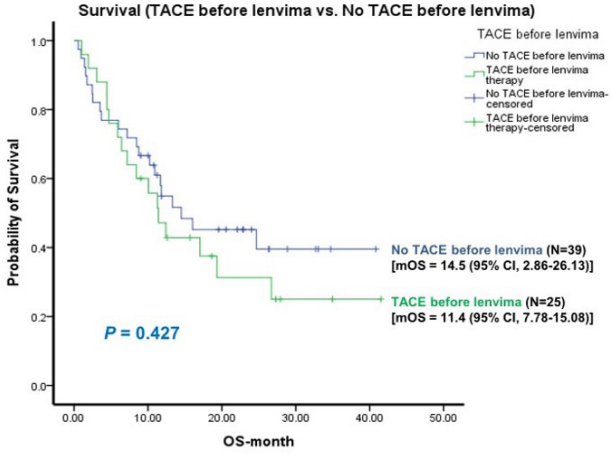
Results: Median age was 59.5 years. 58% were classified as Child-Pugh (CP) A and 37% as CP B, and 5% as CP C. The median OS was 12.4 months. Patients with CP A liver function had significantly longer OS compared to the patients with CP B or C (19.3 vs. 8.4 months, p=0.001). Also, patients with ALBI grade 1 showed better OS compared with patients with ALBI grade 2 or 3 (19.3 vs. 8.5 months, p=0.004). Meanwhile, lower AFP (<200 ng/mL) or PIVKA-II (<100 mAu/mL) level were associated with longer OS. When the patients who received TACE within 1 year before lenvatinib administration were analyzed, OS time was shorter in this group of patients compared to that of the patients without previous TACE (11.4 vs. 14.5 months, p=0.427). Also, patients with main PVTT had significantly

shorter OS compared to patients without major PVTT (27.2 vs. 10.9 months, p=0.000). In multivariate analyses, main PVTT was the only independent factor associated with the survival.

Conclusions: In this real-world study of lenvatinib for HCC patients, REFLECT eligibility criteria, especially absence of main PVTT was the important prognostic factor. Also, TACE prior to lenvatinib has no additional benefit in this high tumor burden HCC patients.

Keywords: Lenvatinib, Hepatocellular carcinoma, Prognosis, Portal vein tumor thrombus





PE-156

Effect of Frailty on Short- and Long-Term Outcomes Following Hepatectomy for Elderly Patients with Hepatocellular Carcinoma: A Multicentre Study

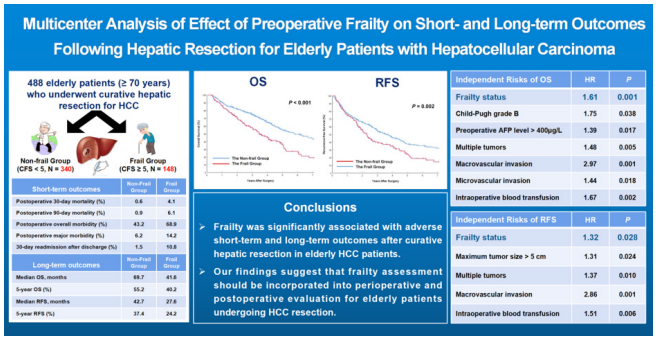
Tian Yang[1,2*], Dan Li[3*], Yong-Kang Diao[2*], Nan-Ya Wang[4*], Yi-Fan Yang[5*], Wei-Min Gu[6], Ting-Hao Chen[7], Jie Li[8], Hong Wang[9], Ya-Hao Zhou[10], Ying-Jian Liang[11], Timothy M. Pawlik[12], Wan Yee Lau[2,13], Feng Shen[2,14], Guo-Yue Lv[1]

[1]Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, First Hospital of Jilin University, Changchun, Jilin, China, [2]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China, [3]Cancer Center, First Hospital of Jilin University, Changchun, Jilin, China, [4]Phase I Clinical Trial Unit, Department of Clinical Research, First Hospital of Jilin University, Changchun, Jilin, China, [5]Department of Hepatobiliary Surgery, Affiliated Hospital of Nantong University, Nantong, Jiangsu, China, [6]The First Department of General Surgery, the Fourth Hospital of Harbin, Harbin, Heilongjiang, China, [7]Department of General Surgery, Ziyang First People's Hospital, Ziyang, Sichuan, China, [8]Department of Hepatobiliary Surgery, Fuyang People's Hospital, Fuyang, Anhui, China, [9]Department of General Surgery, Liuyang People's Hospital, Liuyang, Hunan, China, [10]Department of Hepatobiliary Surgery, Pu'er People's Hospital, Pu'er, Yunnan, China, [11]Department of Hepatobiliary Surgery, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China, [12]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, United States, [13]Faculty of Medicine, the Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China, [14]Eastern Hepatobiliary Clinical Research Institute (EHCRI), Third Affiliated Hospital of Navy Medical University, Shanghai, China

Aims: The growing demand for surgical resection in elderly hepatocellular carcinoma (HCC) patients highlights the impact of preoperative frailty on surgical outcomes. This multicentre cohort study aimed to investigate the association between frailty and short- and long-term outcomes following hepatic resection among elderly HCC patients.

Methods: A multicentre analysis was conducted on elderly HCC patients (≥70 years) who underwent curative-intent resection at 10 Chinese hospitals from 2012 to 2021. Frailty was assessed using the Clinical Frailty Scale (CFS), with frailty defined as CFS ≥ 5. Primary outcomes included overall survival (OS) and recurrence-free survival (RFS); secondary outcomes encompassed postoperative morbidity and mortality. The outcomes between patients with and without preoperative frailty were compared.

Results: Of the 488 elderly patients, 148 (30.3%) were considered frail. Frail patients experienced significantly higher 30-day morbidity (68.9% vs. 43.2%), 30-day mortality (4.1% vs. 0.6%), and 90-day mortality (6.1% vs. 0.9%) than non-frail patients (all p<0.05). During a median follow-up of 37.7 months (interquartile range: 20.4-57.8), frail patients demonstrated significantly worse median OS (41.6 months [95% CI, 32.0-51.2] vs. 69.7 months [55.6-83.8]) and RFS (27.6 months [23.1-32.1] vs. 42.7 months [34.6-50.8]) compared to non-frail patients (both p<0.01). Multivariable Cox regression analysis revealed frailty as an independent risk for decreased OS (HR 1.61, p=0.001) and RFS (HR 1.32, p=0.028).



Conclusions: Frailty was significantly associated with adverse short-term and long-term outcomes after resection in elderly HCC patients.

Our findings suggest that frailty assessment should be incorporated into perioperative and postoperative evaluation for elderly patients undergoing HCC resection.

Keywords: Frailty, Hepatocellular carcinoma, Hepatectomy, Hepatectomy, Recurrence-free survival

PE-157

Development and Validation of Nomograms to Predict Survival and Recurrence Following Hepatectomy for Intermediate/Advanced Hepatocellular Carcinoma: A Multi-Institutional Observational Study

Yong-Kang Diao1,2*, Lan-Qing Yao1,2*, Yong-Yi Zeng3*, Jun Han2,4*, Xiao-Dong Sun1*, Ming-Da Wang2*, Chao Li2, Guang-Zhao Shao1, Li-Hui Gu2, Zhong-Qi Fan1, Wan Yee Lau2,5, Timothy M. Pawlik6, Feng Shen2, Guo-Yue Lv1, Tian Yang1,2,3

[1]Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, First Hospital of Jilin University, Changchun, Jilin, China, [2]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China, [3]Department of Hepatobiliary Surgery, Mengchao Hepatobiliary Hospital, Fujian Medical University, Fuzhou, Fujian, China, [4]Faculty of Hepato-Pancreato-Biliary Surgery, First Medical Center of Chinese PLA General Hospital, Beijing, China, [5]Faculty of Medicine, the Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China, [6]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, United States

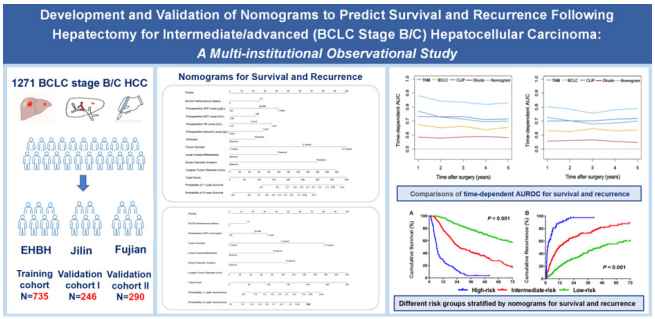
Aims: Despite the Barcelona Clinic Liver Cancer (BCLC) system discouraging hepatectomy for intermediate/advanced hepatocellular carcinoma (HCC), the procedure is still performed worldwide, particularly in Asia. This study aimed to develop and validate nomograms for predicting survival and recurrence for these patients.

Methods: We analyzed patients who underwent curative-intent hepatectomy for intermediate/ advanced HCC between 2010 and 2020 across three Chinese hospitals. The Eastern Hepatobiliary Surgery Hospital (EHBH) cohort was used as the training cohort for the nomograms construction, and the Jilin First Hospital (Jilin) and Fujian Mengchao Hepatobiliary Hospital (Fujian) cohorts served as the external validation cohorts. Independent preoperative predictors for survival and recurrence were identified through univariable and multivariable Cox regression analyses. Predictive accuracy was measured using the concordance index (C-index) and calibration curves. The predictive performance between the nomograms and conventional HCC staging systems was compared.

Results: A total of 1,271 patients met the inclusion criteria. The nomograms for predicting survival and recurrence were developed using 10 and 6 independent variables, respectively. Nomograms' C-indexes in the training cohort were 0.772 (95% CI 0.750-0.794) and 0.723 (95% CI 0.700-0.746) for survival and recurrence, outperforming four conventional staging systems (p<0.001). Nomograms accurately stratified risk into low, intermediate, and high subgroups. These results were validated well by two external validation cohorts.

Conclusions: We developed and validated nomograms predicting survival and recurrence for patients with intermediate/advanced HCC, contradicting BCLC surgical guidelines. These nomograms may facilitate clinicians in formulating personalized surgical decisions, estimating long-term prognosis, and strategizing neoadjuvant/ adjuvant anti-recurrence therapy.

Keywords: Hepatectomy, Barcelona clinic liver cancer, Survival, Recurrence, Prediction model, Nomogram



PE-158

Comparison of Long-Term Clinical Outcomes between Radiofrequency Ablation and Hepatic Resection in Patients with Single Small (≤2 cm) Hepatocellular Carcinoma

Young Mi Hong1, Hwaseong Ryu2, KT Yoon1, Tae Un Kim2

[1]Department of Internal Medicine, Pusan National University College of Medicine, Liver Center, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea, [2]Department of Radiology, Pusan National University College of Medicine, Radiology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea

Aims: Hepatic resection (HR) and radiofrequency ablation (RFA) are currently recommended as an initial curative treatment for early stage hepatocellular carcinoma (HCC). This study aim to compare the long-term clinical outcomes of HR and RFA in patients with single small (≤2 cm) HCC.

Methods: This retrospective study included patients who were newly diagnosed with single small HCC measuring 2 cm or smaller. Overall survival (OS) and recurrence-free survival (RFS) were compared between the HR and RFA group. Prognostic factors for OS and RFS were analyzed by multivariate analysis.

Results: We included 177 patients (101 in the HR group and 76 in the RFA group). The median duration of follow-up for OS and RFS was 85 months and 61 months, respectively. There were no significant differences between the frequency and severity of complications for the two groups. The frequency of recurrence was similar between the two groups. The 3-year, 5-year, and 10-year RFS rates were not significantly different between the HR group and the RFA group (74.7%, 63.0%, 52.9% vs 68.7%, 57.3%, 39.6%, p=0.079). However, OS was significantly higher in the HR group than in the RFA group (p<0.001). The 3-year, 5-year, and 10-year OS rates were 95.0%, 86.1% and 79.9% in the HR group and 80.3%, 71.1% and 48.0% in the RFA group, respectively. Multivariate analysis revealed that patients with HBV infection (HR: 3.55, 95% CI: 1.31–9.64; p=0.013), higher prothrombin-induced by vitamin K absence or antagonist-II (HR: 2.79, 95% CI: 1.15–6.76; p=0.023) and albumin-bilirubin (ALBI) score (HR: 3.01, 95% CI: 1.20–7.57; p=0.019) before treatment had poor OS.

Conclusions: In patients with a single (≤2 cm) HCC, HR was associated with significantly better long-term OS compared with RFA. Moreover, the ALBI score showed significant predictive capabilities for OS.

Keywords: Hepatocellular carcionma, Hepatic resection, Radiofrequency ablation, Prognosis

PE-159

Case Study: Atezolizumab plus Bevacizumab Regimen and Possible Higher Risk of Brain Hemorrhage

Bang Ju Kim, Hyun Joon Park, Kwang Il Seo, Jung Wook Lee, Byung Cheol Yun, Sang Uk Lee

Department of Internal Medicine, Kosin University, Gospel Hospital

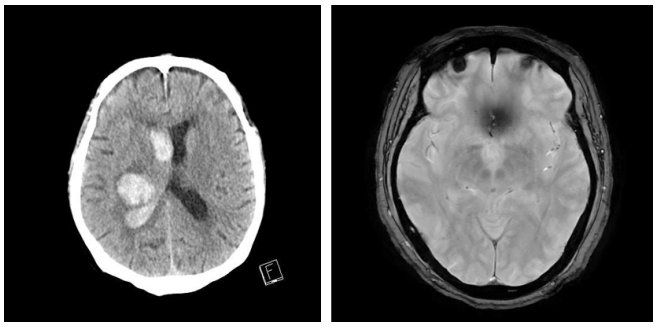
Aims: Atezolizumab plus bevacizumab regimen is used for advanced Hepatocellular carcinoma(HCC). It is shown in many studies that Atezolizumab and Bevacizumab increases the variceal bleeding risk. However, the relevance between Atezolizumab and Bevacizumab regimen and brain hemorrhage is yet unknown. The authors reported two patients who developed brain hemorrhage after AB regimen.

Methods: Two cases were reviewed to find a relevance between brain hemorrhage and AB regimen in advanced HCC patinets

Results: The first patient had been diagnosed with HCC in 2017 without any past histories including hypertension, and received transcatheter arterial chemoembolization 6 times. After 5 years, HCC recurred and the patient received two cycles of AB regimen over the period between November 2022 and December 2022. Two days after the last immunotherapy, the patient came to emergency room with mental change, and then he was diagnosed with intracranial hemorrhage and intraventricular hemorrhage on brain CT. He expired the following day. The second patient was also diagnosed with HCC in 2021, and received liver segmentectomy. The patient had taken a calcium-channel blocker and blood pressure was well-controlled. But HCC was recurred and hepatoduodenal lymph node metastasis was also observed. The patient received transcatheter arterial chemoembolization and radiotherapy. However, HCC recurred 3 months after radiotherapy with multiple distant lymph node metastasis. Then the patient went through two cycles of AB regimen. For surveillance, a brain angiography was performed and an aneurysm in A-comm was found. One day before the scheduled third immunotherapy, the patient came to emergency room with headache. The initial CT scan showed no significant hemorrhage, but the following MRI showed a subtle subarachnoid hemorrhage. And a successful coil embolization was done. Follow up exams showed no further bleeding so far.

Conclusions: These two cases suggest that there are possibilities of not only the high risk of variceal bleeding but also a risk of brain hemorrhage in patients treated with AB regimen in advanced HCC. Moreover, further real-world study about AB regimen with brain hemorrhage would be needed.

Keywords: Hepatocellular carcinoma, Atezolizumab, Bevacizumab, Immunotherapy, Brain hemorrhage



PE-160

Serum AFP Response as a Preoperative Prognostic Indicator in Unresectable Hepatocellular Carcinoma with Salvage Hepatectomy Following Conversion Therapy

Kong-Ying Lin[1,2*], Zhi-Wen Lin[1,2*], Qing-Jing Chen[1,2*], Liu-Ping Luo[1*], Jin-Hong Chen[3], Kui Wang[4], Sheng Tai[5], Zhi-Bo Zhang[2], Shi-feng Wang[6], Jing-Dong Li[7], Kai Wang[8], Lu Zheng[9], Si-Ming Zheng[10], Tian Yang[4#], Yong-Yi Zeng[1,2#]

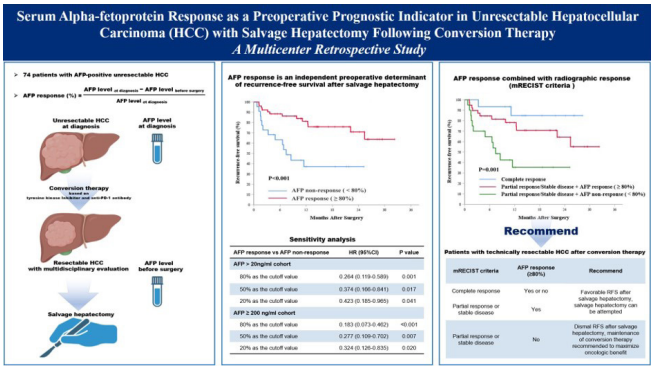
[1]Department of Hepatopancreatobiliary Surgery, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, 350000, China; [2]Department of Hepatopancreatobiliary Surgery, First Affiliated Hospital of Fujian Medical University, Fuzhou, 350000, China; [3]Department of General Surgery, Huashan Hospital, Cancer Metastasis Institute, Fudan University, Shanghai, 200000, China; [4]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Navy Medical University (Second Military Medical University), Shanghai, 200000, China; [5]Department of Hepatopancreatobiliary Surgery, Second Affiliated Hospital of Harbin Medical University, Harbin, Harbin, 150086, China; [6]Department of Hepatopancreatobiliary Surgery, Ganzhou Fifth People's Hospital of Gannan Medical University, Ganzhou, 341000, China; [7]Department of Hepatopancreatobiliary Surgery, The Affiliated Hospital of North Sichuan Medical College, Sichuan, 637000, China; [8]Department of Hepatopancreatobiliary Surgery, Second Affiliated Hospital of Nanchang University, Nanchang, 330006, China; [9]Department of Hepatopancreatobiliary Surgery, Second Affiliated Hospital of Army Medical University, Chongqing, 400037, China; [10]Department of Hepatopancreatobiliary Surgery, First Affiliated Hospital of Ningbo University, Ningbo, 315000

Aims: To evaluate the applicability of alpha-fetoprotein (AFP) response as a surrogate biological marker for determining recurrence-free survival (RFS) in patients with unresectable hepatocellular carcinoma (uHCC) undergoing salvage hepatectomy after conversion therapy of tyrosine kinase Inhibitor (TKI) and anti-PD-1 antibody-based regimen.

Methods: This multicenter retrospective study included 74 patients with uHCC and positive AFP (>20 ng/mL) at diagnosis who underwent salvage hepatectomy after treatment with TKIs and anti-PD-1 antibody-based regimens. The association between AFP response, defined as a ≥ 80% decrease in final AFP (before salvage hepatectomy) from diagnosis, and RFS after salvage hepatectomy was investigated.

Results: Survival analysis showed that AFP responders had better postoperative RFS than non-responders ($p<0.001$). The median postoperative RFS was not reached in the AFP responder group, with a 2-year RFS rate of 70.8%. In contrast, the AFP non-responder group had a median postoperative RFS of 7.43 months, with a 2-year RFS

rate of 37.1%. The multivariate Cox proportional model further identified AFP response as an independent preoperative predictor of RFS (HR, 0.332; 95% CI, 0.129, 0.857; *p=0.023*). Integrating AFP response with radiologic tumor response facilitated further stratification of patients into distinct risk categories: those with complete radiologic response experienced the most favorable RFS, followed by patients with partial response/stable disease and AFP response, and the least favorable RFS among patients with partial response/stable disease but without AFP response. Sensitivity analyses further confirmed the association between AFP response and improved RFS, regardless of using a 50% or 20% cutoff value or in the subgroup of patients with AFP ≥200 ng/ml at diagnosis (all *p<0.05)*.



Conclusions: The "20-80" rule based on AFP response could be helpful for clinicians to preoperatively stratify the risk of patients undergoing salvage hepatectomy, enabling identification and management of those unlikely to benefit from this procedure.

Keywords: Hepatocellular carcinoma, Salvage hepatectomy, Alpha-fetoprotein response, Recurrence-free survival

[Liver Cirrhosis and Portal Hypertension]

PE-161

Non-Invasive Test for Estimation of Liver Fibrosis

Khishgee. D[1], Amarjargal. B[2], Badamsuren. D[3]

[1]Intermed Hospital, Department of Gastroenterology, [2]M.D, Intermed hospital, Department of Gastroenterology, [3]Ph.D, Intermed hospital, Department of Gastroenterology, Mongolia

Aims: Background: In 2015 the digestive disorders were the second leading cause of
morbidity among Mongolian population. The observed mortality from cancer in 2013 was 23.4% including liver cancer which is the first most common cause of cancer death. Furthermore, the digestive disease related death accounts for 4.7% of all mortality. Recently many noninvasive markers for assessing liver fibrosis have been developed, and they are frequently used in clinical practice. FIB4 index had a predictive value to confirm the existence of significant fibrosis with a specificity of 74% and a sensitivity of 70% and APRI score had a sensitivity of 89% and a specificity of 75%.

Methods: Cross sectional study was carried out. A total of 120 patients were enrolled in this study including 40 healthy individuals, 40 patients with chronic viral liver disease and 40 patients with alcoholic liver disease. Complete blood count (PLT), biochemistry (AST, ALT), abdominal ultrasonography were performed. APRI, FIB-4 scores were calculated and compared with the results of the laboratory tests.

Results: A total of 120 patients were enrolled in this study; 40% of patients were males. Their mean age was 43.43±10.93 years. Liver fibrosis stages that are determined by APRI score: FO-1 mild fibrosis accounts for 54.3%, F2-3 moderate fibrosis 40.6%, F4-cirrhosis 11.5%; by FIB4 score: 62.8% was in F0-1, 20.3% was in F2-3, 11.5% was in F4 stage among alcoholic liver disease group. In viral disease group liver fibrosis stages that were evaluated by APRI score were 36.2%-F0-1 mild fibrosis,32.4%-F2-3 moderate fibrosis, 31.4%-F4 severe fibrosis. Statistically significant difference were observed between alcoholic liver disease and viral liver disease groups in liver fibrosis stages that was determined with APRI score ($p<0.05$). In the abdominal ultrasonography increased echogenicity in alcohol group 32.5%, in virus group 52,5%, hepatomegaly in alcohol group 43.6%, vena portae dilated in alcohol group 8.3%, in virus group 10.6%, splenomegaly in alcohol group 14.1%, in virus group 20.1%, splenic vein dilated on alcohol group 20.3%, in virus group 14.75%. Alcohol and viral hepatitis abdominal ultrasonography is a statistically significant difference. In the present study, we found a statistically significant negative correlation between FIB4 score and platelet count, moderate negative correlation between FIB4 score, and albumin, total protein level, weak correlation between alkaline phosphatase, GGT, total bilirubin levels and FIB4 score ($p<0.05$). APRI correlated significantly with AST and ALT levels, whereas platelet count, total protein albumin levels demonstrated moderate negative correlation with APRI scores ($p<0.05$).

Conclusions: 1. The APRI F2-3, the FIB4 F0-1 and F4 scores showed high sensitivity for the diagnosis of alcohol related liver fibrosis. The FIB4 F2-3, F4 score showed high sensitivity for the diagnosis of virus related liver fibrosis. These measures also demonstrated significant correlation with the stage of liver fibrosis in patients with viral hepatitis.
2. For non-invasive diagnosis of liver fibrosis F2-3, using FIB4 was related to necroinflammation, F4 was related with necroinflammation, cholestasis, hypersplenism, liver failure syndromes.

Keywords: Liver fibrosis, Coagulopathy, Liver cirrhosis, APRI, FIB4

PE-162

Clinical Effectiveness of Human Albumin in Liver Cirrhosis: A Meta-Analysis Update

Huijuan Zhou[1], Ziqiang Li[1], Yuhan Liu[2], Daer Dili[2], Qing Xie[1]

[1]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China, [2]Takeda (China) International Trading Co., Ltd, Shanghai, China

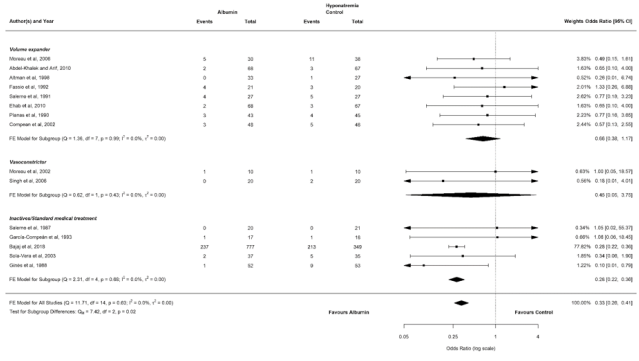
Aims: We examined the clinical effectiveness of albumin infusion to resolve hyponatremia and other complications and compared diverse treatment groups in liver cirrhotic patients.

Methods: Systematic literature search of PubMed and EMBASE for articles reporting clinical effectiveness of albumin infusion in cirrhotic patients was performed from inception till date and registered at PROSPERO (CRD42022372709). For the main meta-analysis, the

studies were pooled, and albumin infusion was compared with control. Subgroup meta-analysis compared albumin infusion and other treatment groups. The odds ratio (OR) and mean difference (MD) estimated the outcome at 95 % confidence interval (CI).

Results: Twenty-two studies were included in the analysis. Pooled data showed an overall significant low incidence of hyponatremia (OR, 0.33; 95 % CI [0.26 - 0.41]), severe infection (OR, 0.52 [0.29 - 0.94]), and post-paracentesis circulatory dysfunction (PICD) (OR, 0.36 [0.21 - 0.61]) with albumin treatment. Among subgroup analysis, statistically significant improvement was observed with albumin infusion vs I/SMT (OR, 0.28 [0.22 - 0.36]), while favorable improvement was observed with volume expander (VE) (OR, 0.66 [0.38 - 1.17]) or vasoconstrictor (OR, 0.45 [0.05 - 3.75]). For PICD, improvement with albumin was significant compared to other VEs (OR, 0.31 [0.15 - 0.63]), but did not reach statistical significance with vasoconstrictor (OR, 0.63 [0.21 - 1.91]). Overall subgroup analysis showed albumin infusion lowered the odds of hyponatremia (OR, 0.33 [0.26 to 0.41]) and PICD (OR, 0.38 [0.21 to 0.69]) significantly. Pooled data showed comparable incidences of peripheral edema (OR, 0.97 [0.55, 1.70]) and overall adverse events (OR, 0.98 [0.92, 1.03]) between albumin and control groups. In-hospital mortality of albumin vs other VE (OR, 1.02 [0.42 to 2.44]) and a favorable improvement when compared to the I/SMT group (OR, 0.58 [0.20 to 1.67]).

Conclusions: Human albumin is beneficial for the treatment of liver cirrhosis patients as it is effective in reducing hyponatremia, PICD and severe infection.



Keywords: Albumin, Efficacy, Hyponatremia, Liver cirrhosis, Safety

PE-163

The Prediction of Liver Decompensation Using Hepatic Collagen Deposition Assessed by Computer-Assisted Image Analysis with Masson's Trichrome Stain

Hae Won Yoo[1], Seon Ah Maeng[1], Ra Kyung Lee[1], Kyung Hun Park[1], Jae Woo Park[1], Min Jung Jung[2] Jeong-Ju Yoo[1], Sang Gyune Kim[1], Young Seok Kim[1]

[1]Digestive Disease Center and Research Institute, Department of Internal Medicine, SoonChunHyang University School of Medicine, Bucheon, Korea, [2]Department of Pathology, SoonChunHyang University College of Medicine, Bucheon, Korea

Aims: The current pathologic system classifies structural deformation caused by hepatic fibrosis semi-quantitatively, which may lead to a disagreement among pathologists. We measured hepatic fibrosis quantitatively using collagen proportionate area (CPA) in compensated cirrhotic patients and assessed its impact on predicting the development of liver decompensation.

Methods: From January 2010 to June 2018, we assessed 101 patients who went through liver biopsy and received diagnosis as compensated cirrhosis with digital image analysis of CPA. Clinical and laboratory data were collected at the baseline and at the time of the last follow-up or progression to liver decompensation (LD).

Results: The mean age was 50.8±10.5 years, and the most common etiology of liver disease was chronic hepatitis B (48.5%), followed by alcoholic hepatitis (18.8%). The mean CPA was 16.91±9.60%. The mean CPA values were different in patients with and without LD development (21.8±11.1 *vs.* 15.2±8.5). During the median follow-up of 60.0 months, 26 out of 101 patients experienced LD. Older age (hazard ratio [HR],1.069; p=0.015), prolonged international normalized ratio (HR, 6.449; p=0.019) and higher CPA (HR, 1.049; p=0.040) were independent predictors of liver decompensation on multivariate cox-regression analysis. When patients were divided according to the optimal CPA threshold (26.8%), higher CPA predicted LD better than lower CPA. (Log-rank test: p<0.001)

Conclusions: CPA could be useful quantitative prognostic value for patients with compensated cirrhosis.

Keywords: Trichrome stain, Hepatitis B, Chronic, Image processing, Computer-assisted, Collagen

PE-164

Machine Learning-Based Classification System for Predicting Liver Fibrosis in Hepatitis C Patients: Enhancing Accuracy and Reducing Invasive Procedures

Rifaldy Fajar[1], Tereza Barbara[2], Kubizek Xeinz[2], Helleni Wohlan Koutakis[1]

[1]Department of Mathematics and Computer Science, Karlstad University, Sweden, and [2]Department of Public Health, Karlstad University, Sweden

Aims: Hepatitis C is a formidable disease characterized by its silent progression, absence of early symptoms, and prolonged treatment duration. Currently, the gold standard for diagnosing liver fibrosis in Hepatitis C patients relies on invasive and expensive liver biopsies, posing significant limitations in terms of patient discomfort, healthcare costs, and accessibility to accurate diagnosis. In light of these challenges, there is a pressing need for a less invasive and cost-effective diagnostic approach. This research presents a groundbreaking solution, a machine learning-based classification system that leverages the power of the Extreme Learning Machine (ELM) algorithm to predict liver fibrosis with remarkable accuracy. The primary objective of this study is to propose an innovative machine learning-based classification system that accurately predicts liver fibrosis in Hepatitis C patients. By developing an alternative to invasive liver biopsies, this approach aims to revolutionize the diagnosis and treatment of Hepatitis C, providing a more patient-friendly and cost-effective solution.

Methods: To improve the accuracy of our classification system, we

employ two powerful techniques: Principal Component Analysis (PCA) feature selection and Synthetic Minority Oversampling Technique (SMOTE). These techniques allow us to optimize the performance and robustness of our approach. To evaluate the effectiveness of our proposed system, we utilize datasets obtained from Hepatitis C patients in both Egypt and Germany. Our study encompasses three key stages: pre-processing, classification, and evaluation. In the pre-processing stage, we apply the min-max scaler algorithm to normalize the data, ensuring that all features are on a consistent scale. Additionally, we address the issue of class imbalance by utilizing the SMOTE oversampling technique, which generates synthetic samples of the minority class, thus creating a balanced training set. For the classification stage, we employ the Extreme Learning Machine (ELM) algorithm, a powerful machine learning technique known for its efficiency and accuracy. To further refine our model, we leverage PCA feature selection, which reduces the dimensionality of the dataset while retaining the most informative features. This step aids in capturing the essential patterns and relationships within the data, leading to improved classification accuracy. In the evaluation stage, we rigorously assess the performance of our ELM-based system using a confusion matrix, which provides valuable insights into the system's ability to correctly classify instances from different classes. By evaluating the system across four distinct scenarios, we obtain a comprehensive understanding of its strengths and limitations.

Results: Our findings showcase a substantial improvement in the accuracy of the classification system when incorporating SMOTE and PCA on the German dataset, yielding an impressive overall accuracy of 99%. This remarkable achievement highlights the potential of our approach to accurately predict liver fibrosis in Hepatitis C patients within the German population. However, it is important to note that the improvement observed in the Egyptian dataset was more moderate, with an overall accuracy of 31%. This discrepancy may be attributed to several factors, including variations in patient demographics, genetic profiles, or differences in healthcare practices and resources. These results underscore the need for further investigation and refinement of our proposed approach to ensure its effectiveness across diverse patient populations.

Conclusions: In conclusion, this study highlights the potential of an ELM-based classification system for accurately predicting liver fibrosis in Hepatitis C patients. By reducing the reliance on invasive liver biopsies, our approach offers an opportunity to improve the diagnosis and treatment of Hepatitis C. The integration of machine learning techniques, such as ELM, PCA feature selection, and SMOTE oversampling, can revolutionize the field of Hepatitis C diagnosis, providing a more accessible and efficient method for healthcare interventions.

Keywords: Classification system, Hepatitis C, Machine learning, Liver fibrosis

PE-165

Prevalence of Helicobacter Pylori Infection among Patients with Liver Cirrhosis in Makassar : A Descriptive Study

Muhammad Ranushar[1], Muhammad Luthfi Parewangi[1], Fardah Akil[1], Nu'man AS Daud[1], Rini Rachmawarni Bachtiar[1], Susanto H Kusuma[1], Amelia Rifai[1], Arifin Seweng[2]

[1]Division of Gastroenterohepatology, Department of Internal Medicine, Faculty of Medicine, Hasanuddin University/HAM Akil Gastoenterohepatology and Endoscopy Center at Wahidin Sudirohusodo Hospital, [2]Department of Biostatistic, Faculty of Public Health, Hasanuddin University, Makassar, Indonesia

Aims: Prevalence of Helicobacter pylori infection in patiens with liver cirrhosis

Methods: A hospital-based cross-sectional study was conducted at The Division of Gastroenterohepatology, HAM Akil Gastoenterohepatology and Endoscopy Center at Wahidin Sudirohusodo Hospital, Department of Internal Medicine Education at Hasanuddin University, Makassar. A total of 245 diagnosed liver cirrhosis patients were included in this study. The duration during the period January 2018 to December 2022.

Results: 245 patients have liver cirrhosis. Subjects aged between 20 and 81 years with a mean of 52.2 11.6 years; the majority (76.6%) were male. The prevalence of Helicobacter pylorii in liver cirrhosis found in the study was 1.6% (4 of 245). Helicobacter pylori prevalence was highest in patients with liver cirrhosis, aged 50–59 years (3.7%). In hepatitis C patients who have liver cirrhosis, the incidence of Helicobacter pylori infection is 15.4%, while in hepatitis B virus infection it is as much as 2%. The mean number of cirrhotic patients infected with Helicobacter pylori were at CTP stage A (3.8%).

Conclusions: The prevalence of Helicobacter pylorii in liver cirrhosis found in the study was 1.6% (4 of 245).

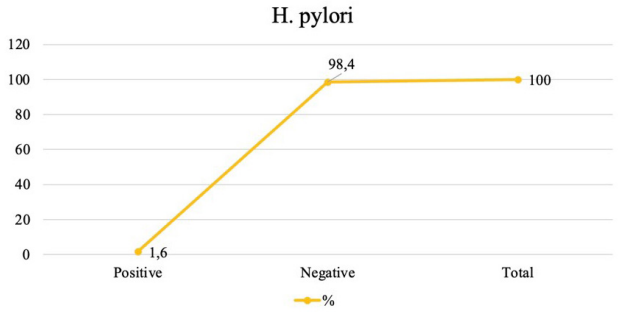


Figure 1. Graph of H. pylori prevalence in patients with liver cirrhosis

Keywords: Helicobacter pylori, Prevalence, Liver cirrhosis, Child-turcotte-pugh (CTP), Hepatitis B virus (HBV), Hepatitis C virus (HCV)

PE-166

Recurrence of Idiopathic Portal Hypertension after Liver Transplantation with Portal Vein Thrombosis and Splenectomy: A Case Report and Review of the Literature

Aibar Aginbay

Department of Hepatology, National Research Oncology Center, Astana, Kazakhstan

Aims: Idiopathic portal hypertension (IPH) is a rare disease characterized by clinical portal hypertension in the absence of a recognizable cause and has a good prognosis, but some cases require liver transplantation

Methods: We report the case of a 32-year-old male patient diagnosed

with IPH 10 years ago. Clinical signs were splenomegaly, leucothrombocytopenia, and esophageal varices. The histology of the liver biopsy showed portal fibrosis with no evidence of incomplete septal cirrhosis. Due to recurrent episodes of bleeding from esophageal varices, despite band-ligations and performed TIPS procedure, cadaveric liver transplantation was performed 6 years ago. Following liver transplantation, the esophageal varices disappeared but splenomegaly and low blood cells leucothrombocytopenia persisted. The immunosuppression composed of prednisolon, tacrolimus. After 3 years increase in portal vein diameter, which reached over 4 in 2022 with the reccurence of esophageal varices, in December there was a thrombosis of the portal vein, complicated by ascites and bleeding. Anticoagulant therapy for 3 months was unsuccessful.

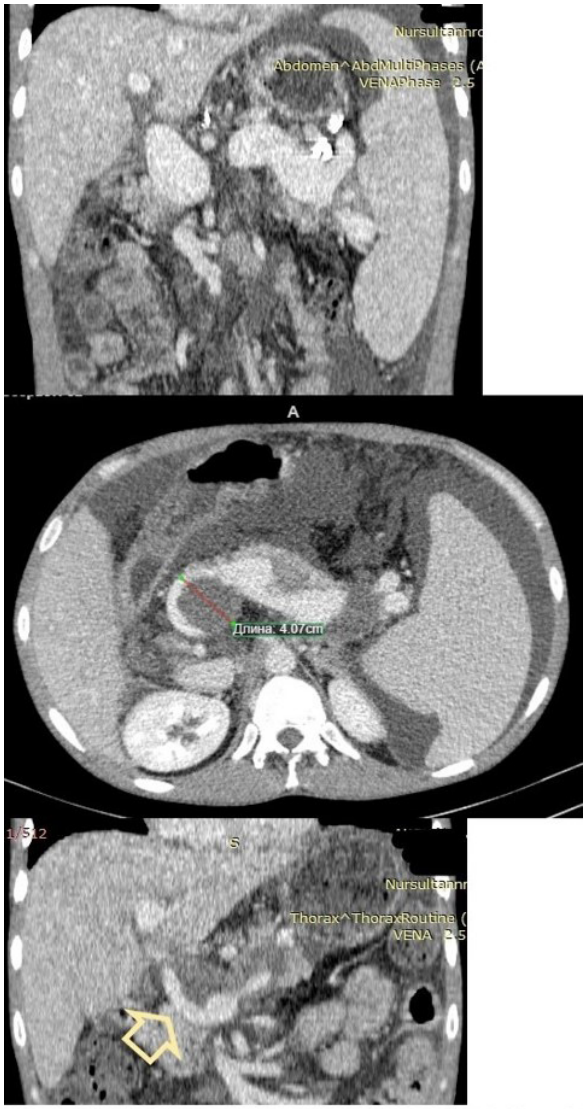


Figure 1. The portal phase of abdominal dynamic CT. a. The abdominal dynamic CT in February 2022 showed portal hypertension without thrombosis; b. Huge portal vein(4cm) with thrombosis before anticoagulation therapy; c. The abdominal dynamic CT reveals the enlargement of portal vein with thrombus in main portal tract and splenic vein after splenectomy.

Results: In April 2023, the patient underwent splenectomy. Histopathologically, the liver had obliterative portal venopathy, nodular regenerative hyperplasia, and incomplete septal cirrhosis.

Conclusions: Liver transplantation may be a curative therapy for patients with advanced disease of IPH but the long-term follow-up after transplantation and we need more information on the benefits of one-stage splenectomy during transplantation.

Keywords: Idiopathic portal hypertension, Liver transplantation, Portal vein thrombosis, Splenectomy

PE-167

Enhancing Bioavailability of Furosemide for the Management of Liver Cirrhosis Using Self Nano Emulsifying Drug Delivery System

Pankajkumar Yadav

Department of Pharmaceutical Sciences, SHUATS, Prayagraj, India

Aims: The objective of this study was to enhance the bioavailability of furosemide (FURO), an antihypertensive loop diuretic used in the management of liver cirrhosis, by improving its water solubility, permeability, and absorption after oral administration. To achieve this aim, a novel drug delivery system, Self Nano Emulsifying Drug Delivery System (SNEDDS), was employed.

Methods: Various oils, surfactants, and co-surfactants were tested to determine their ability to improve the solubility of FURO. The self-emulsification region was identified using pseudoternary diagrams, and SNEDDS formulations were developed accordingly. The formulations were characterized using zeta potential determination, droplet size analysis, dilution test, viscosity determination, *in vitro* dissolution studies, and *in vivo* pharmacodynamic evaluation.

Results: Mean droplet size of the optimized formulation was found to be 26.8 nm. *In vitro* performance of the optimized preparation was satisfactory as observed by various analyses such as dilution test, emulsification time, and precipitation assessment. *In vitro* dissolution studies exhibited that the optimized SNEDDS formulation F3 exhibited a 1.7 fold increase in dissolution efficiency as compared to plain FURO and marketed formulations. *In vivo* studies showed enhanced bioavailability of F3 in terms of diuretic efficacy.

Conclusions: The study confirms the potential use of SNEDDS formulation as an alternative to traditional oral formulations of FURO to enhance its bioavailability in the management of liver cirrhosis.

Keywords: Diuretic, Portal hypertension

PE-168

The Characteristics of Patients with Liver Cirrhosis Who Develop Portal Hypertensive Gastropathy

Ha Linh[1], Nguyen Lan[2], Nguyen Khac Hung Manh[2], Le Quoc Tuan[1]

[1]103 Cam Khe Clinic, [2]Thai Nguyen University of Medicine and Pharmacy, Vietnam

Aims: Portal hypertensive gastropathy (PHG) is a common endoscopic finding in patients with liver cirrhosis (LC). It is a known cause of anemia and acute or insidious gastrointestinal (GI) bleeding as well as esophageal and gastric varices and gastric antral vascular ectasia in these patients. A number of risk factors for PHG have been identified.

Aims: To explore the characteristics of patients with LC who develop PHG.

Methods: This Prospective cross-sectional study was conducted on patients of cirrhosis of liver at hospital, during endoscopic evaluations from May 2019 to April 2022. Clinical findings (age, sex, etiology, the presence of esophageal varices, splenomegaly and severity of LC), laboratory data, PHG was endoscopically graded as absent, mild, or severe.

Results: In a univariate analysis, a younger age, male sex, non-viral etiology, presence of esophageal varices, splenomegaly, severe LC, low platelet count, and low hemoglobin concentration were associated with PHG. A multivariate analysis showed a significant association of PHG with the presence of esophageal varices (p<0.01), non-viral etiology (p<0.05), splenomegaly (p<0.01), and severe LC (p<0.05).
The incidence of esophageal varices were very high. The portal-hypertension gastropathy has a paradoxical correlation with the esophageal variceal grading (OR=0.6). The grade of esophageal varices significantly related to cirrhotic severity according to the Child-Pugh's classification (OR=3.6).

Conclusions: Esophageal varices, splenomegaly, severe liver cirrhosis, and etiology were found to be risk factors for PHG in patients. The percentage of the portal-hypertension gastropathy and gastric varices is not low.

Keywords: Portal hypertensive gastropathy, Liver cirrhosis, Esophageal varices, Splenomegaly

PE-169

Wearable Technology for the Management of Liver Cirrhosis and Hypertension: A New Tool

Deepika Singh, Manvendra Singh

SHUATS, HMFa-MIET, India

Aims: In India, liver cirrhosis and hypertension is a prevalent and important causes of mortality. The treatment of hypertension and liver cirrhosis involves using a therapeutic medication, lowering stress levels, oxygen, and rehabilitation. These complications may be avoided when necessary, by monitoring patients for early indications of liver cirrhosis and hypertension intensification and administering medication. Wearable smartwatches today include functions for heart rate monitoring, liver diseases and cardiovascular disease detection, and health-related information. In this study, we did a feasibility study to investigate the potential use of wearable smart watches to see whether patients regularly wear and retain the devices and whether smart watches properly gather and transmit data from sensors.

Methods: Approximately 135 hypertension and liver cirrhosis s patients took part in the current trial for the whole 60 days. For the current investigation, smartphones and smartwatches from various well-known brands were used. Each patient received a set of wearable devices, and data on heart rate, physical activity, acceleration, questionnaire study, and audio recording were gathered. Patients were instructed to use and charge their smartwatches every day. The wearable device was encouraged to be used frequently by all patients. The following information on associated adherence factors was gathered through the use of demographic characteristics, cardiovascular health assessments, technological fluidity, the Scale Compliance on Hypertensive, and life questionnaires on quality health-related factors. Through the increase in measurement numbers in various circumstances, wearable devices are expected to significantly change the quality of detection and management..

Results: Among 135 patients with hypertension and liver cirrhosis, 110 patients participated, regularly use the watches, and completed the study. The binary models of logistic regression showed that lower compliance with lifestyles, lower compliance with medications, and higher total compliance are important predictors of compliance. Frequent determination of blood pressure measurements and the various features for example environmental monitoring enable data on blood pressure to be interpreted in the context of daily stressors and situations. The heart rate and data of the accelerometer were determined from the devices directly. Secondary results such as questionnaire survey, heart rate, and physical activity were provided with an average day of 60.2, 61.3, and 58.2 respectively. Patients are requested to fill in the feedback on the wearable smart watch devices related to the secondary function of these watches and how the system could be amended and manage their diseses.

Conclusions: We speculated that participants with hypertension and liver cirrhosis continuously wear and use the wearable system and provide positive feedback for this technology. Further study and validation will also be necessary to investigate how this wearable mHealth technology may be helpful to develop better self-management education programs.

Keywords: Liver cirrhosis, Hypertension, Smart watches

PE-170

Evaluation of Spleen Stiffness-Spleen Size-to-Platelet Ratio Score (SSPS) as Non-Invasive Predictor of Oesophageal Varices in Patients with Cirrhosis of Liver

Abhishek Kumar Verma[1], Dibyalochan Praharaj[2], Anil C. Anand[3]

[1]Department of Gastroenterology and Hepatology, Kalinga Institute of Medical sciences (KIMS), Bhubaneswar, Odisha, India, [2,3]Department of Gastroenterology and Hepatology, Kalinga Institute of Medical sciences (KIMS), Bhubaneswar, Odisha, India

Aims: Early diagnosis and evaluation of oesophageal varices (OV) in cirrhosis of liver is crucial before the first variceal bleeding as it is associated with high mortality. As upper GI endoscopy (UGIE) has limitations like being invasive and poor patient compliance, non-invasive methods that can be used for diagnosis of OV needs to be evaluated. Both liver stiffness (LS) and spleen stiffness (SS) can predict OV but are having varied sensitivity and specificity. By combining LSM with spleen size and platelet count (LSPS), the sensitivity of predicting OV improved. There is only one study till date which evaluated combination of SS with spleen size and platelet count (SSPS) as a predictor of OV. Hence this study was aimed to evaluate SSPS as non-invasive predictor of presence and severity of OV.

Methods: This is a prospective cross-sectional study conducted at KIMS, Bhubaneswar, India from April 2021 to March 2023. 132 consecutive patients of compensated cirrhosis of any etiology were included. Clinical evaluation, laboratory investigations, abdominal

ultrasonography, UGIE and FibroScan® were done. SSPS and other non invasive markers like LS, SS, LS+SS and LSPS were calculated.

Results: Mean age was 52.5 years and males were 80.3 %. Most common etiology of cirrhosis was alcohol (68.9%). OVs were present in 52.3% cases and among them, 45% had large varices. Compared to all the noninvasive markers (LSM, SSM,LS+SS and LSPS) studied, SSPS is found to be most accurate for both diagnosis (AUROC 0.997, sensitivity 97.1, specificity 98.41% and accuracy was 97.7%) and grading of OV (AUROC, 0.941, sensitivity 93.55, specificity 86.14 and accuracy was 89.5%.)

Conclusions: SSPS is found to be good predictor for diagnosing and grading of OV and hence can be used as a screening test for predicting the presence and the severity of OV.

Keywords: SSPS, Oesophageal varices, Non invasive predictors, Cirrhosis of liver

Table 1 : ROC analysis of different parameters for presence of oesophageal varices

Variables	Cut off value	AUROC	P value	Sensitivity	Specificity	PPV	NPV	Accuracy	95% Confidence interval [b]
Liver stiffness	>26.9	0.847	<0.0001	62.32, 95% CI (49.8-73.7)	100, 95% CI (94.3-100)	92	70.8	80.3	0.774 to 0.904
Spleen stiffness	>40.5	0.955	<0.0001	76.81, 95% CI (65.1-86.1)	100, 95% CI (94.3-100)	95	79.7	87.8	0.904 to 0.983
LS + SS	>62.2	0.934	<0.0001	81.16, 95% CI (69.9-89.6)	95.24, 95% CI (86.7-99.0)	94.9	82.2	87.9	0.970
LSPS	>2.47	0.978	<0.0001	88.41,95% CI (78.4-94.9)	98.41, 95% CI (91.5-100.0)	98.4	88.6	93.2	0.937 to 0.996
SSPS	>3.75	0.997	<0.0001	97.1,95% CI (89.9-99.6)	98.41, 95% CI (91.5-100.0)	98.5	96.9	97.7	0.967 to 1.000

Table: 2 ROC analysis of different parameters for presence of large oesophageal varices

Variables	Cut off value	AUROC	P value	Sensitivity	specificity	PPV	NPV	Accuracy	95% Confidence interval [b]
Spleen stiffness	>47.8	0.944	<0.0001	98.0, 95% CI (88.8-100.0)	100.0, 95% CI (96.4-100.0)	92.1	98.3	95.3	0.972 to 1.000
Liver stiffness	>27.6	0.908	<0.0001	90.0, 95% CI (88.8-100.0)	90.1, 95% CI (82.5-95.1)	75.6	97.6	94.5	0.953 to 0.999
LSPS	>3.58	0.947	<0.0001	96.77, 95% CI (83.3-99.9)	84.16, 95% CI (75.6-90.7)	65.2	98.8	89.8	0.894 to 0.978
SSPS	>6.61	0.941	<0.0001	93.55, 95% CI (78.6-99.2)	86.14, 95% CI (77.8-92.2)	67.4	97.8	89.5	0.886 to 0.974
LS + SS	>80	0.957	<0.0001	92, 95% CI (88.8-100.0)	100, 95% CI (96.4-100.0)	94.6	95.4	90.6	0.801 to 0.937

PE-171

Risk Factor of Portal Hypertension in Children with Biliary Atresia

Rendi Aji Prihaningtyas, Firyal Nadiah Rahmah, Anindya Kusuma Winahyu, Bagus Setyoboedi, Sjamsul Arief

Child Health Department, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Aims: Biliary atresia is a serious hepatobiliary disease and frequently results in portal hypertension. This study aims to analysed risk factors of porta hypertension in children with biliary atresia.

Methods: A case-controlled study was performed for 96 children with biliary atresia. Subject were enrolled based on the inclusion and exclusion criteria. Inclusion criteria including biliary atresia. Subject suffered from congenital anomaly and sepsis was excluded. The follow-up starts from January 2022 and period ended May, 2023. Medical history, physical examination results, imaging data, and laboratory examination results were collected prospectively. This study was approved by ethical committee Dr. Soetomo General Academic Hospital, Surabaya. Patients were divided into two groups based on the sign of porta hypertension clinically during follow-up period, based on whether they had porta hypertension. Risk factors for porta hypertension were analysed using SPSS. Univariate analysis was used first to identify possible risk factors. A multivariate analysis was performed using logistic regression with *p* significant <0.05.

Results: The average age was 18,21 (3,14-128,86) weeks in porta hypertension group and 9,07 (1,00-50,57) weeks in non-porta hypertension group. Age, duration of illness, birth weight, gestational age, and laboratory examination (Hb, WBC, Albumin, Direct bilirubin, Total bilirubin, PPT, GGT, AST, AST: ALT, AST:ALT ratio, and CRP) were significant differences in both group (p<0,05). For every one-week increase in the subject's age, the risk of portal hypertension increased by 1.127. For every one unit increase in Hb, PPT, GGT, and the AST:ALT ratio, the risk of becoming portal hypertension was 0.746, 1.125, 1.00, and 2.862 in children with atresia (p<0,05).

Conclusions: The risk factors for portal hypertension in children with biliary atresia include age, Hb levels, PPT levels, GGT levels, and the AST:ALT ratio. Periodic evaluation of laboratory tests is very important to monitor the occurrence of complications due to biliary atresia.

Keywords: Biliary atresia, Porta hypertension, AST, ALT

Table 1. Basic characteristic of the subjects

Variable	Case (Portal Hypertension)	Control (Non-Porta Hypertension)	p
Sex			0,99[a]
Male	23 (47,90)	32 (66,70)	
Female	25 (52,10)	16 (33,30)	
Birth			0,03[a]
Premature	4 (8,30)	13 (27,10)	
Aterm	44 (91,70)	35 (37,90)	
Kasai operation			0,03[a]
Yes	8 (16,70)	1 (2,10)	
No	40 (83,30)	48 (97,90)	
Liver biopsy			0,00[a]
Fibrosis	24 (77,40)	8 (33,30)	
No Fibrosis	7 (22,60)	16 (66,70)	
	Median (Min. – Max.)	Median (Min. – Max.)	
Age (week)	18,21 (3,14-128,86)	9,07 (1,00-50,57)	0,00[b]
Onset of jaundice (week)	4,00 (1,00-20,00)	2,00 (1,00-8,00)	0,09[b]
Duration of illness (week)	12,57 (1,71-117,43)	5,86 (0,00-49,57)	0,00[b]
Birth weight (gram)	3.050,00 (1.800,00-4.200,00)	2.900,00 (900,00-3.900,00)	0,03[b]
Gestational age (week)	38,50 (36,00-41,00)	38,00 (32,00-41,00)	0,00[b]

[a]Chi square test; [b]Mann-whitney test; p significant < 0,05

Table 2. Laboratory Examination of the Subjects

Variable	Case (Portal Hypertension)	Control (Non-Porta Hypertension)	p
Hb (g/dL)	9,80 (5,20-15,80)	11,45 (5,90-21,50)	0,00[a]
WBC	13.565,00 (4.450,00 – 27.900,00)	11.120,00 (5.730,00-28.430,00)	0,01[a]
Platelet (10^3/µL)	305.271,00 ± 204,48	351.437,00 ± 226,08	0,29[b]
Albumin (g/dL)	3,29 (1,80-4,40)	3,80 (2,33-4,32)	0,03[a]
Direct bilirubin (mg/dL)	9,36 (1,16-22,05)	6,10 (1,10 -23,29)	0,00[a]
Total bilirubin (mg/dL)	12,57 (5,80-34,06)	8,55 (1,90-33,25)	0,00[a]
APTT (s)	33,3 (11,40-73,20)	34,10 (16,70-48,30)	0,28[a]
PPT (s)	13,30 (0,00 -121,40)	11,45 (0,00-23,80)	0,00[a]
GGT (U/L)	360,00 (37,02-2.386,00)	148,50 (23,90-1261,00)	0,00[a]
AST (U/L)	237,00 (100,00-1.642,00)	177,50 (29,90-5.775,00)	0,02[a]
ALT (U/L)	140,00 (35,00-505,00)	140,10 (22,30-3.284,00)	0,65[a]
AST:ALT ratio	1,70 (0,54-4,51)	1,31 (0,38-4,52)	0,02[a]
GGT:AST ratio	1,58 (0,08-15,1)	0,76 (0,04-9,92)	0,99[a]
GGT:ALT ratio	3,44 (0,17-15,2)	1,35 (0,08-12,4)	0,02[a]
CRP (mg/dL)	0,80 (0,10-6,40)	0,15 (0,09-18,61)	0,00[a]

[a]Mann-whitney test; [b]Independent Sample T test; p significant < 0,05

Table 3. Multivariate analysis of risk factors forPorta Hypertension

Variable	p	OR	95% confidence interval for OR
Age (week)	0,006[a]	1,127	1,035 – 1,227
Hb (g/dL)	0,015[a]	0,746	0,590 – 0,944
PPT (s)	0,027[a]	1,125	1,013-1,249
GGT (U/L)	0,006[a]	1,000	1,001-1,005
AST:ALT ratio	0,028[a]	2,862	1,124-7,289

[a]logistic regression; p significant < 0,05

PE-172

Characterisitcs of Cirrhotic Patients in Indonesia: A Literature Review

Hadi Saputra[1], Rinita Istiqomah[2]

[1]Muhammadiyah Surakarta University, [2]Yogyakarta State University, Indonesia

Aims: Liver cirrhosis is one of the diseases that absorbs the most of the Health Insurance Fund budget in Indonesia, where in 2020 the Health Social Security Administration Agency reported 156,764 cases of liver cirrhosis with a budget absorption of IDR 243.5 billion. Liver cirrhosis is a chronic liver disease caused by various factors such as infection by hepatitis B virus, hepatitis C and alcohol. This study aims to determine the characteristics of patients with liver cirrhosis in Indonesia.

Methods: This research is a literature review study using various related journals, which were published in 2013 to 2022. The research used is quantitative research with descriptive tests and chi square tests.

Results: The main clinical features of patients with liver cirrhosis who were hospitalized were mostly males (67.7%), aged between 51-60 years (34.3%), the majority of high school education level (61.61%), etiology due to hepatitis B virus (60.7%), with classification Child-Pugh C (61.5%), the most common comorbid disease was sepsis (6.3%), ascites and abdominal distension (20%) is a clinical picture that often arise, increased AST (15%) and loss of albumin and hemoglobin (16%) is the laboratory results that often abnormal, and most complications are esophageal varices (23.5%), and there was a significant relationship between the Child-Pugh score (p=0.001), comorbid sepsis (p=0.000), complications of hepatic encephalopathy (p=0.001) with possible risk factors for death in patients with liver cirrhosis.

Conclusions: Cirrhosis affects mostly males, aged between 51-60 years, the majority of high school education level, HBV infection is the most common, with classification Child-Pugh C, the most common comorbid disease was sepsis, ascites and abdominal distension as common clinical features, increased SGOT and a decrease in albumin and hemoglobin as the most common abnormal laboratory picture.

Keywords: Liver cirrhosis, Characteristics

PE-173

Direct/Total Bilirubin Ratio as a Risk Factor of Portal Hypertension

Firyal Nadiah Rahmah[1], Rendi Aji Prihaningtyas, Bagus Setyoboedi[2], Sjamsul Arief

Child Health Department, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Background: Cholestatic jaundice in infancy, indicated by conjugated hyperbilirubinemia, is a complex diagnostic problem that indicates hepatobiliary and/or metabolic dysfunction. Of the various conditions that can present neonatal cholestasis, biliary atresia represents the major cause with a common consequence of portal hypertension which can lead to significant morbidity and mortality. The direct/total bilirubin ratio can be used to distinguish the causes of jaundice in many patients who have increased levels of bilirubin. However, the reference range of the direct/total ratio has not been established, hindering its clinical usefulness. This study assessed the use of direct/total bilirubin ratio in predicting portal hypertension among cholestatic infants.

Methods: This case-control study involved cholestatic infants between the age of 2 weeks to 2 years old admitted to Dr. Soetomo General Academic Hospital. Cholestatic infants with and without portal hypertension were then classified as case and control group, respectively. Sample cases in this study were drawn from the total population, with the inclusion criteria infants who had cholestasis, and exclusion criteria that include infants who had congenital or genetic disorders. Samples were taken by purposive control. Demographic, clinical and laboratory data obtained were then summarized and analyzed by univariate and bivariate analysis using SPSS ver. 25.

Results: The number of cases and control group that met the inclusion criteria were 48 patients, respectively. Of 96 cholestatic patients, 55 were male (57.3%) and 41 were female (42.7%). Regarding the finding of liver biopsy, higher incidence of fibrosis was found in cholestatic patients with portal hypertension (p<0.05). Moreover, higher direct and total bilirubin were significantly found in cholestatic patients with portal hypertension (p<0.05). Direct/total bilirubin ratio is a risk factor of portal hypertension among cholestatic infants (OR 0,005; 95% CI 0,000-0,569).

Conclusions: To conclude, the current study suggests that the possibility of portal hypertension is increasing 0.005 times for every increase of 1 unit of direct/total bilirubin ratio among cholestatic infants (p<0.05). However, additional studies are required to validate these findings.

Keywords: Neonatal cholestasis, Direct bilirubin, Total bilirubin, Direct/total bilirubin ratio

Variable	Case (Portal Hypertension)	Control (Non-Porta Hypertension)	P
Sex Male Female	 23 (47,9) 25 (52,1)	 32 (66,7) 16 (33,3)	0,99 chi square test
Acholid stool Yes No	 38 (79,2) 10 (20,8)	 21 (43,8) 27 (56,3)	0,001
Dark urine Yes No	 14 (29,2) 34 (70,8)	 26 (54,2) 22 (45,8)	0,023
Liver biopsy Fibrosis No Fibrosis	 24 (77,4) 7 (22,6)	 8 (33,3) 16 (66,7)	0,003
Liver biopsy Intrahepatic cholestasis Extrahepatic cholestasis	 3 (9,7) 20 (90,3)	 13 (61,9) 8 (38,1)	0,000
Age (week)	18,21 (3,14-128,86)	9,07 (1,0-50,57)	0,00 Mann-whitney test

Laboratory Examination

Variable	Case (Portal Hypertension)	Control (Non-Porta Hypertension)	P
Hb (g/dL)	9,80 (5,2-15,8)	11,45 (5,9-21,5)	0,000
WBC	13565 (4450 – 27900)	11120 (5730-28430)	0,01
Platelet	305271 ± 204,48	351437 ± 226,08	0,29 independent sample T test
SGOT	237 (100-1642)	177,5 (29,9-5775,0)	0,02
SGPT	140 (35,0-505,0)	140,1 (22,3-3284,0)	0,65
Albumin	3,29 (1,8-4,4)	3,8 (2,33-4,32)	0,03
Direct bilirubin	9,36 (1,16-22,05)	6,10 (1,1 -23,29)	0,00
Total bilirubin	12,57 (5,8-34,06)	8,55 (1,9-33,25)	0,00
IgG Toxoplasma Grey zone Reactive Non-reactive	 8 (22,9) 6 (17,1) 21 (60)	 3 (7,5) 7 (17,5) 30 (75)	0,164 Pearson Chi-Square
IgG Toxoplasma Grey zone Reactive Non-reactive	 0 (0,0) 11 (30,6) 25 (69,4)	 0 (0,0)3 1 (2,5) 39 (97,5)	0,00 Continuity Correction[b]
IgG CMV Grey zone Reactive Non-reactive	 0 (0,0) 40 (100) 0 (0,0)	 0 (0,0) 44 (95,7) 2 (4,3)	0,497 Fisher's Exact Test
IgM CMV Grey zone Reactive Non-reactive	 2 (5,0) 20 (50) 18 (45)	 0 (0,0) 16 (34,8) 30 (65,2)	0,063 Fisher's Exact Test
IgG Rubella Grey zone Reactive Non-reactive	 7 (18,4) 0 (23,7) 22 (57,9)	 8 (18,6) 18 (41,9) 17 (39,5)	0,182 Pearson Chi-Square
IgM Rubella Grey zone Reactive Non-reactive	 0 (0,0) 5 (13,2) 33 (86,8)	 0 (0,0) 3 (7,1) 39 (92,9)	0,467 Fisher's Exact Test

PE-174

Evaluation of Spleen Stiffness and Liver Stiffness as Non-Invasive Predictors of Oesophageal Varices in Patients with Cirrhosis of Liver

Abhishek Kumar Verma[1], Dibyalochan Praharaj[2], Anil C. Anand[3]

[1]Department of Gastroenterology and Hepatology, Kalinga Institute of Medical sciences (KIMS), Bhubaneswar, Odisha, India, [2]Department of Gastroenterology and Hepatology, Kalinga Institute of Medical sciences (KIMS), Bhubaneswar, Odisha, India, [3]Department of Gastroenterology and Hepatology, Kalinga Institute of Medical sciences (KIMS), Bhubaneswar, Odisha, India

Aims: This study was done to determine the accuracy of liver stiffness(LS) and spleen stiffness(SS) as non-invasive predictors of presence and grade of OV.

Methods: This is an observational prospective cross-sectional study conducted on 132 patients of compensated cirrhosis of any etiology were included. Clinical evaluations, laboratory investigations, abdominal ultrasonography, UGIE and FibroScan® (for LSM and SSM) were done. Other non-invasive markers like APRI, FIB 4, PSR, LSPS, SSPS were calculated.

Table 1 ROC analysis of different parameters for presence of oesophageal varices

Variables	Cut off value	AUROC	P value	Sensitivity	Specificity	PPV	NPV	Accuracy	95% Confidence interval [b]
Spleen stiffness	>40.5	0.955	<0.0001	76.81, 95% CI (65.1-86.1)	100, 95% CI (94.3-100)	100	79.7	87.8	0.904 to 0.983
Liver stiffness	>26.9	0.847	<0.0001	62.32, 95% CI (49.8-73.7)	100, 95% CI (94.3-100)	100	70.8	80.3	0.774 to 0.904
APRI	>0.9	0.875	<0.0001	75.36,95% CI (63.5-84.9)	87.3, 95% CI (76.5-94.4)	86.7	76.4	81.1	0.806 to 0.926
FIB 4	>3.17	0.865	<0.0001	71.01,95% CI (58.8-81.3)	90.48, 95% CI (80.4-96.4)	89.1	74	80.3	0.795 to 0.918
LSPS	>2.47	0.978	<0.0001	88.41,95% CI (78.4-94.9)	98.41, 95% CI (91.5-100.0)	98.4	88.6	93.2	0.937 to 0.996
SSPS	>3.75	0.997	<0.0001	97.1,95% CI (89.9-99.6)	98.41, 95% CI (91.5-100.0)	98.5	96.9	97.7	0.967 to 1.000
LS + SS	>62.2	0.934	<0.0001	81.16, 95% CI (69.9-89.6)	95.24, 95% CI (86.7-99.0)	94.9	82.2	87.9	0.878 0.970

Table: 8 ROC analysis of different parameters for presence of large oesophageal varices

Variables	Cut off value	AUROC	P value	Sensitivity	specificity	PPV	NPV	Accuracy	95% Confidence interval [b]
Spleen stiffness	>47.8	1.000	<0.0001	100.0, 95% CI (88.8-100.0)	100.0, 95% CI (96.4-100.0)	100	100	100	0.972 to 1.000
Liver stiffness	>27.6	0.989	<0.0001	100.0, 95% CI (88.8-100.0)	90.1, 95% CI (82.5-95.1)	75.6	100	94.5	0.953 to 0.999
LSPS	>3.58	0.947	<0.0001	96.77, 95% CI (83.3-99.9)	84.16, 95% CI (75.6-90.7)	65.2	98.8	89.8	0.894 to 0.978
SSPS	>6.61	0.941	<0.0001	93.55, 95% CI (78.6-99.2)	86.14, 95% CI (77.8-92.2)	67.4	97.8	89.5	0.886 to 0.974
LS + SS	>80	1.000	<0.0001	100, 95% CI (88.8-100.0)	100, 95% CI (96.4-100.0)	100	100	100	0.801 to 0.937

Results: Mean age was 52.5 years and males were 80.3 %. Most common aetiology of cirrhosis was alcohol (68.94%). OVs were present in 52.3% cases and among them 45% had large varices. The cut-off value for the presence of OV was 26.9kPa for LS (AUROC:0.847,Sn:63.3%,Sp:100%) and 40.5kPa for SS (AUROC:0.955,Sn:76.81%,Sp:100%). The cut off values for presence of large OV were 27.6kPa and 47.8kPa for LS(AUROC:0.989,Sn:100%,Sp:90.1%) and SS(AUROC:1.0,Sn:100%,Sp:100%) respectively. Both LSM and SSM could accurately predict the presence and severity of OV with SSM being superior to LSM in terms of AUROC and sensitivity. Among other non-invasive parameters, only APRI and FIB-4 were found to be good predictors for OV. All the three combination markers that is LSPS, SSPS and combination of LS and SS were found to be very good predictors of presence and severity of OV and were found to be superior in predicting OV than either LSM and SSM alone. Among all the parameters studied SSPS is found to be most accurate predictor for OV.

Conclusions: In our study, both LSM and SSM were significantly associated with the presence and severity of varices with SSM corre-

lating better than LSM. Other noninvasive scores like APRI, FIB-4, LSPS, SSPS, combination of LSM and SSM also are proved to be effective predictors. Hence these parameters can be used as screening tests to predict OV in CLD.

Keywords: Liver stiffness, Spleen stiffness, Oesophageal varices, Cirrhosis of liver

PE-175

The Efficacy and Safety of Endoscopic Variceal Ligation versus Propranolol as Prophylaxis of First Variceal Bleeding in Patients with Liver Cirrhosis

Sung Hwan Yoo, Hyun Woong Lee, Jung Il Lee

Department of Internal Medicine, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea

Aims: Both endoscopic variceal ligation and propranolol are known to be effective methods for preventing variceal bleeding, but there are still few published data for comparing efficacy and safety. We analysed the efficacy and safety of endoscopic variceal ligation (EVL) and propranolol in terms of prophylaxis for the first bleeding rate.

Methods: A retrospective cohort study was conducted in 1,052 cirrhotic patients with no history of previous esophageal bleeding with F2 or F3 esophageal varices from a university hospital between September 2008 and October 2022. 697 patients received EVL and 355 patients used propranolol. The primary end-point of the study was bleeding rate and secondary end-point was overall survival.

Results: Life-time table curves indicated that prophylactic EVL and propranolol were similarly effective for primary prophylaxis of variceal bleeding (147/697 [21%] vs 82/355 [23%], p=0.72) and overall mortality (279/697 [40%] vs 128/355 [36%], p=0.46). The 2-year cumulative mortality rate was 31%(217/697) in the EVL group and 27%(97/355) in the propranolol group. Comparison of Kaplan-Meier curves of the time to death of both groups showed no significant difference in mortality in both groups (p=0.78). Patients undergoing EVL died mainly of hepatic failure and propranolol group died mainly from infection.

Conclusions: Both prophylactic EVL and propranolol are effective and safe methods for reducing the incidence rate of first variceal bleeding and mortality.

Keywords: Endoscopic variceal ligation, Propranolol, Prophylaxis

PE-176

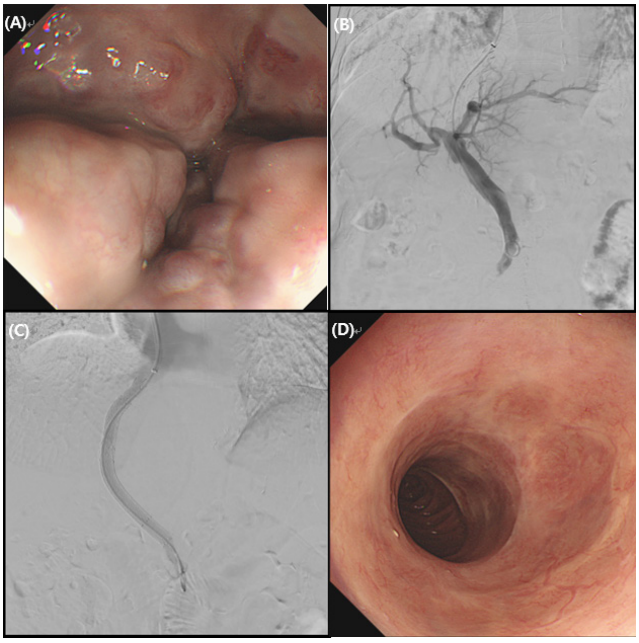
TIPS Is More Useful for the Treatment of Intractable Variceal Bleeding in Patients with Total Gastrectomy

Kyeongsoo Kim, Dahee Kim, Dongyune Ahn, Yunjin Jeong, Hoongil Jo, Eunyoung Cho

Department of Internal Medicine, Wonkwang University School of Medicine and Hospital

Aims: A 65-year-old man was admitted to the emergency room with hematochezia twice a day. Esophageal varix bleeding occurred repeatedly 3 years ago and was treated with EVL twice, and prophylactic EVL was additionally applied three times. A total gastrectomy was performed for gastric cancer 8 years ago, and he was diagnosed with alcoholic liver cirrhosis 10 years ago and treated with medication. At admission, vital signs were BP 110/70mmHg, BT 37 , PR 80/min, RR 16/min, and mental status was alert. Blood tests showed Hgb 8.8 g/dL, WBC 4440/uL, platelet 169,000/uL, PT 14.3 sec, and liver function tests were all normal findings. Considering the past history, the possibility of esophageal varix bleeding was high, therefore upper GI endoscopy was performed. On endoscopy, a bluish-reddish linear protruded vessel with a bleeding spot along with a previous ligation scar was identified mid to distal esophagus and around the surgical margin.

Methods: We performed endoscopic variceal ligation, but it was not effective due to severe scar changes in the surroundings of bleeding spots. Also, we could not continue the endoscopy due to worsened the patient's conditions (cyanosis on the face, a deep drowsy mental status, and SBP of 40mmHg).
We performed intubation, S-B tube insertion, and use of an inotropic agent. The next day, the gastro renal shunt was confirmed by abdominopelvic CT, and TIPS with self-expandable bare stent (epic 10mm x 10cm) was performed through it. Pre-procedural Pressure Gradient was 20 mmHg, post-procedure Pressure Gradient was 12mmHg, which confirmed a significant decrease in HVPG. After the TIPS, the patient improved without additional GI bleeding and was discharged on 7 hospital days. After 1 month of TIPS, upper GI endoscopy confirmed that varix had completely disappeared.
In abdominopelvic CT performed 6 months after TIPS, partial instent thrombosis was suspected in the mid portion of the stent. However, the patient refused both the endoscopy and the TIPS revision and decided to observe because of no symptoms. One year after TIPS, upper GI endoscopy revealed that esophageal varix deteriorated to F3 and a red spot was observed (Fig. A). TIPS revision was performed.



Results: On the pre-procedure portogram, TIPS total occlusion with eccentric thrombosis at main portal vein Fig. B) was confirmed and

pre-procedural Pressure gradient was 26.5 mmHg. We performed dilatation at the occlusion site using a covered stent and Mustang balloon catheter (Fig. C). After revision, we confirmed that the pressure gradient was significantly reduced to 3.5mmHg. In addition, an upper GI endoscopy performed after TIPS revision confirmed that esophageal varix had completely disappeared (Fig. D).

Conclusions: Therefore, TIPS is more useful for the treatment of intractable variceal bleeding in patients with total gastrectomy.

Keywords: TIPS, Esophageal variceal bleeding, Total gastrectomy

PE-177

Prognostic Value of Nutritional Index in Patients with Decompensated Cirrhosis: A Single-Center Cohort Study

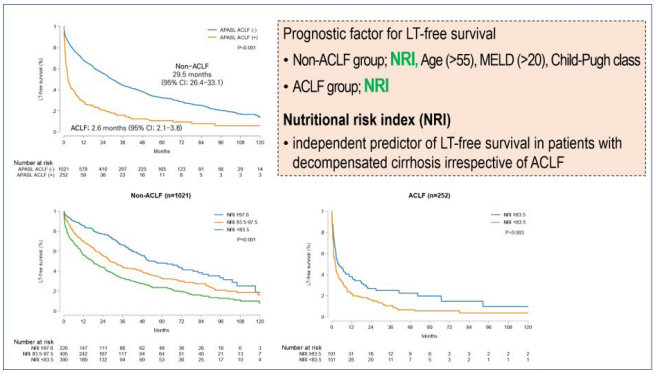
Heechul Nam[1,2], Hee Yeon Kim[1,2], Chang Wook Kim[1,2*]

[1]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]The Catholic Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Nutritional assessment is critical in patients with decompensated liver cirrhosis to maintain quality of life and improve survival. Nevertheless, the predictive value of nutritional index for the outcome of decompensated cirrhosis remains uncertain. This study aims to determine the potential prognostic value of nutritional index in predicting the liver transplantation (LT)-free survival of decompensated cirrhosis.

Methods: This is a single-center, retrospective study that included consecutive patients presenting with first-onset decompensated complications to Uijeongbu St. Mary's Hospital from January 2013 to December 2022. Nutritional assessment in this study utilized the nutritional risk index (NRI), which was calculated based on serum albumin levels, body weight, and height. The primary end point was LT-free survival.

Results: The study included 1273 patients, with a median age of 57 years, of whom 69.5% were male. Alcoholic-related liver disease was the most common cause of liver disease in this cohort (65.2%), followed by chronic hepatitis B (15.9%), nonalcoholic steatohepatitis (11.6%), chronic hepatitis C (3.7%), and autoimmune hepatitis or primary biliary cholangitis (3.5%). The median MELD score of the patients was 16 (IQR, 12-22), and 19.8% of them met the criteria for APASL ACLF. At the time of the first admission, the most common complications observed were ascites (71.2%), followed by variceal bleeding (52.2%), hepatic encephalopathy (26.6%), spontaneous bacterial peritonitis (5.4%), and hepatorenal syndrome (11.8%). The median LT-free survival was 22.2 months (95% CI; 18.7-25.6 months). We conducted analysis based on ACLF; ACLF group (n=1021) and non-ACLF (n=252). The median LT-free survival was 29.5 months (95% CI, 26.4-33.1) in the non-ACLF group and 2.6 months (95% CI, 2.1-3.8) in the ACLF group (*p<0.001), respectively. In the non-ACLF group, Age ≥55 (HR, 1.53; 95% CI, 1.30-1.80, p*<0.001), MELD ≥20 (HR, 1.63; 95% CI, 1.33-2.04, *p*<0.001), Child-Pugh class C (HR, 1.94; 95% CI, 1.42-2.65, *p*<0.001), and NRI ≤83.5 (HR, 1.61; 95% CI, 1.23-2.10, *p*<0.001) were identified as independent predictors of LT-free survival. In the ACLF group, NRI ≤83.5 (HR, 1.47; 95% CI, 1.10-1.96, *p*=0.010) was only independently associated with LT-free survival.



Conclusions: In conclusion, nutritional index is independent predictor of LT-free survival in patients with decompensated cirrhosis irrespective of ACLF. Integrating nutritional index with established prognostic factors may improve prognostic accuracy and guide treatment decisions.

Keywords: Liver cirrhosis, Nutritional index, Acute-on-chronic liver failure, Liver transplantation

PE-178

Successful Treatment of Refractory Hepatic Encephalopathy with Two Sessions of Plug-Assisted Retrograde Transvenous Obliteration: A Case Report

Yong Soo Song, Seo Jin Yeong, Jae Hyun Yoon, Sung Bum Cho, Sung Kyu Choi

Department of Gastroenterology and Hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea

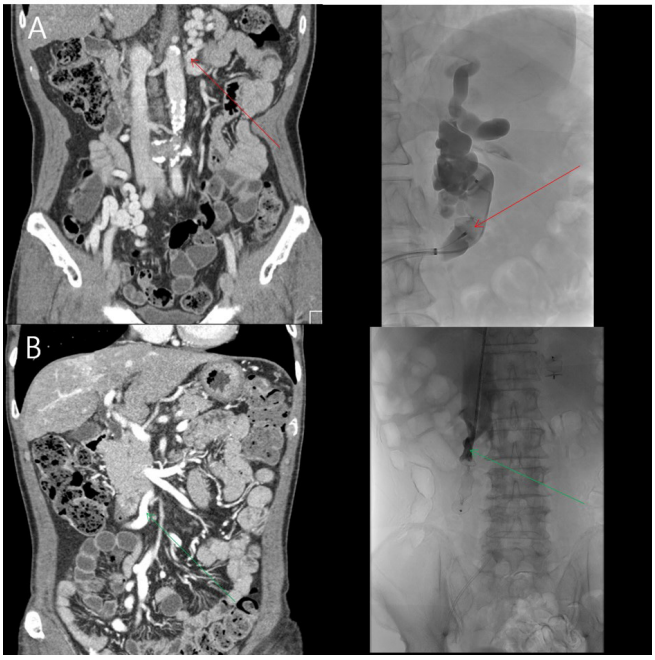
Aims: Hepatic encephalopathy (HE) is a complication of liver cirrhosis implying poor prognosis. Although lactulose is the mainstay of HE management, patients exhibit refractory HE despite medical management especially in group of patients with large spontaneous portosystemic shunt (SPSS). Large SPSS allows the escape of ammonia-rich blood without detoxification in liver causing refractory HE. Despite limited data, plug-assisted retrograde transvenous obliteration (PARTO) of SPSS has been reported as effective modality for HE treatment. However, more than 50% of patients undergo recurrence of HE after PARTO. Herein, we report a case of patient with recurred refractory HE after initial PARTO who was successfully managed with additional sessions of PARTO.

Methods: Case: A 59-year old male was transferred to emergency department due to semi-comatose mentality. The patient had underlying liver cirrhosis by chronic hepatitis C and alcohol and he had achieved sustained virological response of hepatitis C virus 8 months ago and was on abstinence for 6 months. There were no sign of acute infarction or brain hemorrhage at brain computed tomography (CT), and with the level of serum ammonia (201 ㎍/dL) we diagnosed the patients as HE. At laboratory exam, serum level of total bilirubin, albumin and prothrombin time was 1.27mg/dL, 2.6g/dL, and 1.48 (INR), respectively. After two times of lactulose enema, patient's men-

tality was fully recovered. Seven months later, patient had another episode of severe HE and 12mm width gastrorenal shunt was noted at dynamic abdominal computed tomography. We performed PARTO for repeated type B HE and procedure related complication or additional event of HE did not occur. However, after 11 months of initial PARTO, 7 times of refractory and repeated HE recurred with interval of less than 4 weeks. Hence, we underwent additional PARTO for remaining mesocaval shunt of 9mm. Patient has been followed-up for 24 months and HE of any stage did not recur.

Results: Our case implies that even at recurrence of HE after initial PARTO, additional obliteration of SPSS with PARTO can effectively manage refractory HE. Regarding high recurrence of HE after PARTO, 2nd session of PARTO can be considered as rescue therapy.

Conclusions: Our case implies that even at recurrence of HE after initial PARTO, additional obliteration of SPSS with PARTO can effectively manage refractory HE. Regarding high recurrence of HE after PARTO, 2nd session of PARTO can be considered as rescue therapy.



Keywords: Hepatic encephalopathy, PARTO

PE-179

Acute Kidney Disease is Common and Associated with Poor Clinical Outcomes in Cirrhotic Patients with Acute Kidney Injury

Jeong Eun Song, Chang Hyeong Lee, Bung Seok Kim

Department of internal medicine, Daegu Catholic University School of Medicine, Daegu

Aims: Acute kidney disease (AKD) is the persistence of acute kidney injury (AKI) for up to 3 months, which is proposed to be the time-window where critical interventions can be tried to change clinical outcomes of AKI. In cirrhosis, AKD and its impact on outcomes have been insufficiently evaluated. We aimed to investigate the incidence and clinical outcomes related to AKD in patients with cirrhosis and AKI.

Methods: Cirrhotic patients, who were hospitalized from January 2014 to December 2020 at Dagu Catholic University Hospital, were assessed for AKI and AKD, and followed-up for 180 days. AKI, AKD and CKD were defined based on KDIGO and ADQI AKD and renal recovery consensus criteria, respectively. The primary outcome was mortality at 90 and 180 days, and the secondary outcome was de novo chronic kidney disease (CKD).

Results: Of the 392 hospitalized patients with cirrhosis, AKI developed in 36.4% (n=143). AKD occured in 32.9% (n=47) of AKI patients. The cumulative incidence of mortality was significantly higher in patients with AKD compared to to those without AKD: 90-day 12.8% vs. 61.7%, 180-day 17.7% vs. 68.8% (p<0.001). On multivariable analysis, patients with AKD had higher risk of mortality at 90 dyas (hazard ratio [HR] 7.73; 95% CI 3.00-19.92; p<0.001) and 180 days (HR 7.45; 95% CI 3.178-17.49; p<0.001). The incidence of de novo CKD was 14.9% of AKD patients, but there was no occurence of de novo CKD in patients without AKD.

Conclusions: AKD develops in about 1 in 3 hospitalized cirrhotic patients with AKI and it is related to worse survival and de novo CKD.

Keywords: Liver cirrhosis, Acute kidney injury, Acute kidney disease

PE-180

Risk Factors of Bloodstream Infection after Endoscopic Injection of N-Butyl-2-Cyanoacrylate for Gastric Variceal Bleeding

Ui Hyung Kim[1], Hee Yeon Kim[1], Chang Wook Kim[1], Hyo-Jin Lee[2]

Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, Republic of Korea

Aims: Gastric variceal bleeding is associated with a high mortality rate, and sclerotherapy using N-butyl-2-cyanoacrylate is the treatment of choice. We aimed to evaluate the frequency and risk factors of bloodstream infection following the injection of N-butyl-2-cyanoacrylate in a real-world setting.

Methods: We analyzed retrospective data from a single-center cohort of patients with liver cirrhosis who underwent N-butyl-2-cyanoacrylate injection for the treatment of bleeding gastric varices from January 2010 to March 2021. Common skin contaminants were counted as contaminants unless blood cultures were positive on two separate occasions or if there were clinical signs of infection. Recurrent bacteremia was defined as repeated bacteremia caused by the same microorganism after the resolution of the first event occurring at least two weeks from the date of the final positive blood culture of the first event. We excluded patients with a follow-up duration of fewer than 3 weeks.

Results: We included 193 patients with liver cirrhosis and gastric variceal bleeding who received 298 sessions of N-butyl-2-cyanoacrylate injection. All patients received antibiotics prophylaxis; third-generation cephalosporins were used. The average age of patients was 60.0±12.3 years and the mean Model for End-Stage Liver Disease (MELD) score was 13.5±5.4. Of the patients following cyanoacrylate injection, 60 patients developed bacteremia at a median of 323 (inter-

quartile range, 66–932) days from N-butyl-2-cyanoacrylate injection. On multivariate Cox regression analysis, the MELD score [HR 1.05 (1.00–1.1), p=0.04], mean injection volume of N-butyl-2-cyanoacrylate [HR 1.48 (1.09–2.03), p=0.01], and presence of hepatocellular carcinoma [HR 2.38 (1.33–4.26), p=0.003] were statistically significant factors for bacteremia. Nine out of 60 patients developed recurrent bacteremia following sclerotherapy with N-butyl-2-cyanoacrylate. Gram-positive bacterial bloodstream infection was 64.7% in non-recurrent bacteremia, but only 22.2% cases of gram-positive bloodstream infection in recurrent bacteremia (p=0.044). More than half of 60 cases with bacteremia were resistant to third-generation cephalosporin antibiotics.

Conclusions: Bloodstream infection occurred in 31.1% of cirrhotic patients following cyanoacrylate injection for the treatment of gastric variceal bleeding. The MELD score, mean injection volume of N-butyl-2-cyanoacrylate, and presence of hepatocellular carcinoma were predictive factors of bacteremia after the first N-butyl-2-cyanoacrylate injection.

Keywords: Bacteremia, Histoacryl, Varix bleeding

PE-181

Prediction of Portal Hypertension Using Non-Invasive Parameters: Using 670 Cirrhosis Patients' Data

Jong Wan Lim[1], Seul Ki Han[1,3], Taesic Lee[2,3,4], Myung Jae Seo[2,3], Moon Young Kim[1,3*]

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju 26411, Korea, [2]Department of Family Medicine, Yonsei University Wonju College of Medicine, Wonju 26411, Korea, [3]Regenerative Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju 26411, Korea, [4]Division of Data Mining and Computational Biology, Institute of Global Health Care and Development, Wonju 26411, Korea

Aims: Increased portal pressure drives poor outcomes in cirrhosis, prediction of portal hypertension (PH) is essential in management of cirrhosis. Hepatic venous pressure gradient (HVPG) is the gold standard for the estimation of PH however, it is invasive and has limitation in routine clinical application. We developed non-invasive PH prediction model using non-invasive parameters based on 670 patients' HVPG data.

Methods: The variable was categorized into continuous or categorical variables using class function in R Base package. Based on unbiased manner, HVPG and candidate features were entered into univariate linear regression (LiR) as independent and dependent variables. Next, specific cut-offs, including actual p-value or top ranking based on its ascending ordering, were applied to select the HVPG-related variables.

To obtain the generalized finding, random sampling validation was used. The dataset was randomly divided into training and testing datasets with ratio of 0.7 to 0.3. The feature selection and establishment of HVPG estimation model was conducted exclusively using the training dataset. Performance measurement was conducted using the testing dataset. The tasks, including the random dataset split, feature selection, and establishment of HVPG prediction model were iterated at 50 times, yielding fifty lists of the candidate predictors and estimated HVPG values of testing dataset.

Figure

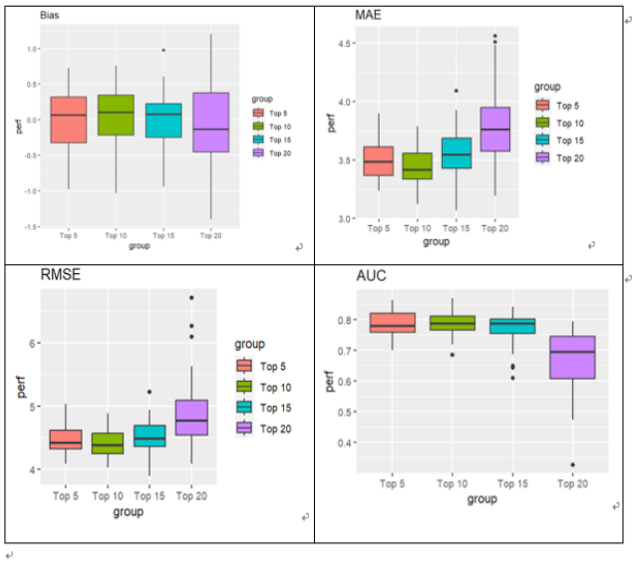


Figure 1. HPVG model including top 10 predictors proposed the best accuracy.

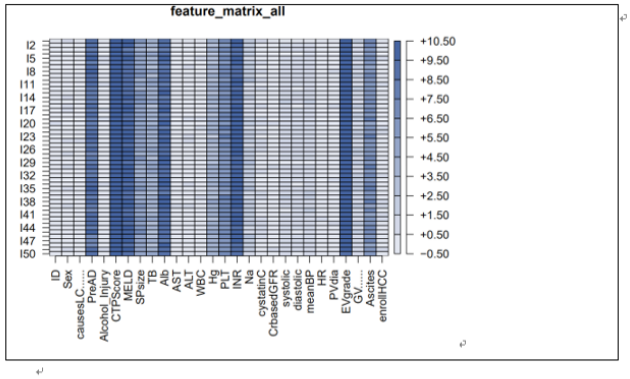


Figure 2. 10 different p-values as feature selection cut-offs. As a result, Pre AD (history of previous decompensation), CTP Score, MELD score, serum albumin, INR, and EV grade were identified as robust predictors for HPVG.

Results: According to the rank-based manner, top 10 features provided the best performance among four cases (top 5, top 10, top 15, and top 20, Figure 1). We set 10 different p-values as feature selection cut-offs, yielding ten lists of feature selection matrix (Figure 2). As a result, Pre AD (history of previous decompensation), CTP Score, MELD score, serum albumin, INR, and EV grade were identified as robust predictors for HPVG. Using this model composed of 10 categories, clinically significant portal hypertension predictive power was reported to be AUROC 0.75 or higher.

Conclusions: Increased portal pressure can be accessed by non-invasive parameters.

Keywords: Portal hypertension, Liver cirrhosis

PE-182

Different Risk Factors of Clinical Outcomes between Variceal Bleeding and Non-Variceal Gastrointestinal Bleeding in Acutely Decompensated Cirrhosis

Ji Won Park[1], Jung Hee Kim[1], Do Seon Song[2], Jang Han Jung, Hyoungsu Kim[1], Eileen L. Yoon[3], Young-Kul Jung[4], Ki Tae Suk[1], Jae-Young Jang[5], Dong Joon Kim[1], Sung-Eun Kim[1*], on behalf of the Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

[1]Department of Internal Medicine, Hallym University College of Medicine, [2]Department of Internal Medicine, Catholic University of Korea College of Medicine, [3]Department of Internal Medicine, Hanyang University College of Medicine, [4]Department of Internal Medicine, Korea University College of Medicine, [5]Department of Internal Medicine, Soonchunhyang University College of Medicine

Aims: Gastrointestinal bleeding (GIB) including variceal bleeding (VB) and non-variceal gastrointestinal bleeding (NVB) is a major complication in patient with chronic liver disease, especially liver cirrhosis. Recent studies reported that there were no differences in clinical outcomes between VB and NVB. However, larger scale, multicenter, prospective studies were warranted to confirm these results because there was different pathogenic mechanism of development between VB and NVB. We aimed to investigate differences of clinical outcomes and risk factor in cirrhotic patients with GIB.

Methods: The prospective Korean Acute-On-Chronic Liver Failure (KACLiF) cohort consisted of 1,773 patients who were hospitalized with acute decompensation of chronic liver disease, from July 2015 to August 2018. We enrolled a total of 490 cirrhotic patient with GIB after excluding non-cirrhotic patients. Patients were then regularly evaluated for adverse outcomes (liver transplantation and death) every 3 month during follow-up period.

Results: A total of 490 cirrhotic patient with GIB were included, 414 with VB and 76 with NVB. Patients with NVB had poorer underlying liver function than those with VB (bilirubin 4.49±3.96 vs 2.86±3.64 mg/dL, p<0.001; Child-Pugh score 8(5-14) vs 7(5-15), p<0.001; MELD 16.6(7-41) vs 13.6(7-54), p=0.004; MELD-Na 19.2(8-41) vs 15.3 (7-50), p<0.001). Patients with VB and NVB had similar 28-day adverse outcome (death or liver transplantation) (4.6% vs 6.6%, p=0.460), 90-day adverse outcome (7.5% vs 13.2%, p=0.101), 1-year adverse outcome (18.4% vs 19.7%, p=0.177). MELD was only one predictor for 28-day, 90-day, and 1-year adverse outcome in patients with VB if factors were analysed with ACLF. However, cardiac failure and/or respiratory failure were additional risk factors for 28-day, 90-day, and 1-year adverse outcomes in patients with VB if factors were analysed each statistically important organ failure. Compared to results in patients with VB, MELD was an important predictor for 28-day and 90-day adverse outcomes in patients with NVB.

Conclusions: Our results showed no statistically difference of adverse outcomes in cirrhotic patients with VB and NVB. However, there were differences of major predictor for short-term and long-term adverse outcomes between patients with VB and NVB.

Keywords: Cirrhosis, Acute decompensation, Variceal bleeding, Acute on chronic liver failure

PE-183

Safety of Warfarin and Direct Oral Anticoagulants in Liver Cirrhosis with Atrial Fibrillation

Yeo Wool Kang, Yang Hyun Baek, Sang Yi Moon

Department of Internal Medicine, Dong-A University college of Medicine

Aims: The safety of anticoagulant therapy in patients with non-valvular atrial fibrillation (AF) and liver cirrhosis (LC) is an important consideration, as these patients are at an increased risk of both thromboembolic events and bleeding complications. While the use of warfarin has been extensively studied in this population, the safety of direct oral anticoagulants (DOACs) in patients with AF and LC is still an area of ongoing research. This study aimed to evaluate the safety of DOACs by comparing the risk of bleeding events in a cohort of patients with cirrhosis and AF.

Methods: We retrospectively analyzed data from 146 patients with both AF and LC who were treated at Dong-A University Hospital from 2015 to May 2020. The patient cohort included 146 individuals with both AF and LC. Among them, 88 patients did not receive any medication, while 58 patients were prescribed medication. The medication group was further divided into two subgroups: the DOAC treatment group and the warfarin treatment group. The primary outcome of interest in this study was the occurrence of major bleeding events. Major bleeding events typically involve significant bleeding, such as intracranial hemorrhage or gastrointestinal bleeding.

Results: The study included 146 patients with both AF and LC, with a mean age of 67.2 years. Out of these patients, 105 (66.7%) were male. Among the 146 patients, 88 (60.3%) did not receive any medication, while 58 (39.7%) were prescribed medication. Within the medicated group, 44 patients (53.8%) were administered DOACs, and 14 patients (46.2%) received warfarin. Major bleeding events were observed in 4 patients (27.3%) in the no-drug group, 3 patients (14.2%) in the warfarin group, and 6 patients (13.6%) in the DOAC group. Gastrointestinal bleeding was the most common type of major bleeding event observed. The cumulative risk of major bleeding did not show a significant difference between the warfarin and DOAC treatment groups, based on Student's unpaired t-test (p=0.469).

Conclusions: This study's findings suggest that there was no statistically significant difference in the incidence of bleeding events between warfarin and DOACs in patients with both AF and LC, regardless of the presence of cirrhosis. This indicates that the choice of anticoagulant medication (warfarin or DOACs) did not significantly influence the risk of bleeding in this particular patient population. Additionally, the study did not find any evidence to suggest that DOACs increased the risk of major bleeding events compared to warfarin treatment. Therefore, the safety profile of DOACs, in terms of major bleeding risk, was similar to that of warfarin in patients with AF and LC. It is important to consider the limitations of the study, such as the relatively small sample size and the fact that it was conducted at a single institution. These limitations may affect the generalizability of the findings to a larger population. Consequently, further research is necessary to confirm these results and provide more robust evidence regarding the safety of anticoagulant therapy in patients with both AF and LC.

Keywords: Liver cirrhosis, Atrial fibrillation, Direct oral anticoagulants, Warfarin

Table1. Clinical and demographic characteristics of the patients

	All	No drug	warfarin	DOAC			
Patients characteristics							
				Dabigatran	Edoxaban	Rivaroxaban	Apixaban
Total, n	146	88	14	7	16	3	18
Sex, n (%)							
Male		67 (76)	7 (50)	7 (100)	13 (81)	2 (67))	9 (50)
Female		21 (23)	7 (50)	0	3 (19)	1 (23)	9 (50)
Bleeding event, n (%)							
Brain hemorrhage		0	2 (14)	1 (14)	1 (6)	0	0
Gastrointestinal bleeding		4 (4.5)	1 (7)	1 (14)	2 (12)	0	1 (6)
Liver function state, n							
Child-Pugh score A		76	12	6	15	3	15
Child-Pugh score B		10	2	1	1	0	3
Child-Pugh score C		2	0	0	0	0	0

PE-184

Different Role of Organ Failure according to Clinical Presentation in Acutely Decompensated Cirrhosis

Jung Hee Kim[1,2], Do Seon Song[3], Ji Won Park[1,2], Jang Han Jung[1,2*], Hyoungsu Kim[1,2], Eileen L. Yoon[4], Tae Hyung Kim[5], Young-Kul Jung[5], Ki Tae Suk[1,2], Jae-Young Jang[6], Won Kim[7], Dong Joon Kim[1,2], Sung-Eun Kim[1,2*], on behalf of the Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

Department of Internal Medicine, Hallym University College of Medicine

Aims: The acute on chronic liver failure (ACLF) is major poor prognosis factor in acute decompensation (AD) of chronic liver disease (CLD) or liver cirrhosis (LC). Main pathogenic mechanism of AD has been speculated systemic inflammation and portal hypertension. The effects of not only ACLF but also each organ failure may be different depending on the major pathogenesis in AD patients, but studies for this have not yet been investigated. Therefore, we aimed to investigate whether significant differences of adverse outcomes (death or LT) show or not according to main clinical presentation in AD cirrhotic patients in prospective Korean Acute-On-Chronic Liver Failure (KACLiF) cohort. Also, we intend to reveal risk factor including ACLF and each organ failure for adverse outcome.

Methods: The prospective KACLiF cohort consisted of 1773 patients who were hospitalized with AD of CLD, from July 2015 to August 2018. We enrolled a total of 1,416 patient with AD after excluding non-LC patients. Patients were then regularly evaluated for 3 months outcomes (liver transplantation and death) at 1 year were also recorded.

Results: According to clinical presentation, patients were analyzed: gastrointestinal bleeding (GIB) (n=490), ascites (n=355), bacterial infection (n=103), hepatic encephalopathy (HEP) (n=178), and jaundice (n=290). The adverse outcomes rate for subgroups of AD were differed as followed; 28-day adverse outcome (total=8.1%, GIB=4.9%, ascites=9.6%, bacterial infection=13.6%, HEp=10.1%, and jaundice=8.3%; p=0.011), 90-day adverse outcome (total=13.5%, GIB=8.4%, ascites=15.2%, bacterial infection=19.4%, HEp=17.4%, and jaundice=15.5%; p=0.001), and 1-year adverse outcome (total 21.9%, GIB=14.7%, ascites=25.1%, bacterial infection=31.1%, HEP=27%, and jaundice=23.8%; p<0.001). After multivariate cox regression analysis, MELD was most important risk factor for adverse outcome in total or subgroup of AD patients if it were analyzed with ACLF. As a result of analysis with each organ failure as a variable other than ACLF, cardiac failure in GIB patients, coagulation failure in ascites patients, coagulation failure and brain failure in BI patients, liver failure in HEP patients, and MELD and DM in jaundice patients were the main factors.

Conclusions: According to main clinical presentation, cirrhotic patients with AD showed different 28-days, 90-days, and 1-year adverse outcomes. Although ACLF is a factor influencing the patient's adverse outcomes, the relevant organ failure may differ depending on the patient's major clinical presentation upon admission. Especially, AD patients with bacterial infection showed poorer adverse outcomes compared to patients with other clinical presentation. Each organ failure rather than ACLF tends to have a direct impact on the prognosis of cirrhotic patient with AD according to the main clinical presentation.

Keywords: Organ failure, Acute decompensation, Cirrhosis, Prognosis

PE-185

MicroRNA-101-3p: A Dual Function Regulator in the Therapeutic Potential of Human Bone Marrow-Derived Mesenchymal Stem Cells for Liver Fibrosis

Seawon Hwang[1], Jung Hoon Cha[2], Na Ri Park[2], Gi Jin Kim[4], Si Hyun Bae[2,3*]

[1]Division of Hospital Medicine, Department of Internal medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 03382, Republic of Korea, [2]The Catholic University Liver Research Center, Department of Biomedicine & Health Sciences, College of Medicine, The Catholic University of Korea, Seoul, 06591, Republic of Korea, [3]Division of Gastroenterology and Hepatology, Department of Internal medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, 03382, Republic of Korea, [4]Department of Biomedical Science, CHA University, Seongnam 13488, Republic of Korea

Aims: Although the precise mechanisms of bone marrow-derived mesenchymal stem cells (BM-MSCs) in liver fibrosis remain unclear, they play crucial therapeutic roles in this condition. Furthermore, microRNAs (miRNAs) are regulators in hepatic differentiation and liver fibrosis. miR-101-3p is upregulated during hepatic trans-differentiation, whereas miR-101-3p is downregulated in a stage of liver fibrosis. The purpose of this study is to investigate miR-101-3p's roles in the hepatic differentiation of human BM-MSC (hBM-MSCs) and hepatic stellate cell (HSC) activation.

Methods: miRTarBase and miRDB were used to predict targets EZH2 of miR-101-3p selected next-generation sequencing. hBM-MSC was treated with miR-101-3p mimic, inhibitor, or EZH2 siRNA during the hepatic differentiation. hHSC LX2 was treated with TGF-β1 and with or without miR mimic and siRNA. BM-MSCs and PRL-1(+) BM-MSCs were injected into the tail vein in the BDL rat model. The role of miR-101-3p was identified through the change of liver-specific genes, EMT markers, and fibrosis genes using quantitative real-time PCR and western blotting.

Results: miR-101-3p showed a higher expression level in the PRL-1(+) BM-MSCs transplantation group than the BDL group and in differentiated hepatocyte-like cells than hBM-MSC but lower expression level in fibrosis than the normal liver. miR-101-3p caused the

increase in the liver-specific genes in hBM-MSC, while mesenchymal markers, fibrosis markers, and apoptosis inhibitor genes decreased in LX2. At this time, the expression of EZH2 has reduced, and the same result as miR-101-3p overexpression was obtained by knockdown of EZH2. As a result, miR-101-3p mimic promoted the hepatic differentiation of hBM-MSC and inhibited the TGF-β1 mediated LX2 activation via regulating EZH2.

Conclusions: In this study, we have identified miR-101-3p as a regulator of hepatic differentiation in hBM-MSCs and a potential mediator of hepatic fibrosis. Our results demonstrate that miR-101-3p may be a biomarker, monitoring the response to therapeutic effect by BM-MSC in liver fibrosis.

Keywords: Human bone marrow-derived mesenchymal stem cells, Hepatic differentiation, Next-generation sequencing, microRNAs, Liver fibrosis

PE-186

Development of a Self-Management Scale for Patients with Liver Cirrhosis

Oh Young Kwon[1], Yeonsoo Jang[2,*], JuHee Lee[2], Sanghun Ahn[3,4], Hye Won Lee[3,4], Hyerang Kim[5]

[1]College of Nursing and Brain Korea 21 FOUR Project, Yonsei University, Seoul, Republic of Korea, [2]College of Nursing and Mo-Im Kim Nursing Research Institute, Yonsei University, Seoul, Republic of Korea, [3]Department of Internal Medicine, College of Medicine, Yonsei University, Seoul, Republic of Korea, [4]Yonsi Liver Center, Severance Hospital, Seoul, Republic of Korea, [5]Department of Nursing Science, Vision college of Jeonju, Jeollabuk-do, Republic of Korea, *Corresponding Author

Aims: Liver cirrhosis is one of the representative chronic liver diseases, being known as a disease with severe and potentially life-threatening complications. Self-management is important to maintain and improve patients' lives, health, and well-being. However, there was a lack of scales to assess the comprehensive aspects of self-management among these patients. This study aimed to develop and validate a self-management scale for patients with liver cirrhosis for measuring the self-management level.

Methods & Results: This study was conducted between June and December 2022 using the data from cirrhotic patients at a tertiary hospital in Seoul. The initial items derived from a literature review and in-depth interviews with 10 individuals with cirrhosis were validated by 10 experts and a preliminary survey was conducted. For construct validity, 295 patients participated and the data were used for exploratory factor analysis and confirmatory factor analysis. Reliability test and concurrent validation was evaluated using Cronbach's alpha and the correlation coefficient between the developed self-management scale and the Chronic Disease Self-Efficacy Scale, respectively.

Conclusions: The proposed self-management scale for patients with liver cirrhosis consisted of five factors with 21 items, with scoring based on a 5-point Likert scale. This scale will be useful for identifying the self-management level of patients with liver cirrhosis and developing strategies to improve the self-management behaviors of this population.

Keywords: Liver cirrhosis, Self-management, Self-management, Exploratory factor analysis

PE-187

Platelet/Spleen Ratio as Non-Invasive Predictor of Esophageal Varices in Cirrhotics

Rakesh Garlapati, V Venkata Ranga Reddy, G Mohan Reddy

Department of Gastroenterology, Kurnool Medical college, Kurnool, India

Aims: To correlate platelet count, spleen diameter, and their ratio with the presence of oesophageal varices in patients with cirrhosis of the liver without any previous evidence of GI bleeding.

Methods: The study was carried out in the Department of Gastroenterology, Government general hospital, Kurnool medical college, Kurnool, Andhra Pradesh. A total of 102 Consecutive patients who were diagnosed to have liver cirrhosis were included Descriptive cross-sectional study. Platelet count was done. Spleen diameter was evaluated using USG abdomen and endoscopy was done to check for varices. Platelet count to spleen bipolar diameter ratio was calculated.

Results: In the studied population, 88.2% had varices on upper GI endoscopy and 11.8% were without varices. Mean platelet count was lower in patients with varices (99643.06±15432.133) than in those without varices (113583.33±15432.133). There was a statistically significant difference. Mean spleen bipolar diameter was higher in patients with varices (128.02±9.303) than in those without varices (114.42±7.44). There was a statistically significant difference. Mean platelet count to spleen diameter was lower in patients with varices (786.462±148.6) than in those without varices (995.868±175.99). There was a statistically significant difference found between mean platelet count to spleen bipolar diameter and varices. ROC curve was applied to platelet count to spleen diameter in determining the presence of varices. The cut off <962.4 had a sensitivity of 84.4% and specificity of 75% with AUC 0.811 95% CI (0.722-0.882).

Conclusions: Platelet count, a simple, inexpensive, and readily available test, The spleen bipolar length is a visually appealing and easily accessible measurement that can be used to predict the development of varices. The platelet count/spleen diameter ratio appears to be a good determinant of portal hypertension. For the detection of varices, the "platelet count/spleen diameter ratio method" appears to be more cost-effective than the "scope all strategy."

Keywords: Cirrhosis, Esophageal varices, Platelet count, Spleen diameter

PE-188

Spleen Stiffness as a Non-Invasive Test to Evaluate Esophageal Varices Needing Treatment and Portal Pressure Gradient in Liver Cirrhosis

Jeong-Ju Yoo[1*], Sun Ah Maeng[1*], Young Chang[2], Sae Hwan Lee[3], Soung Won Jeong[2], Jae Young Jang[2], Gab Jin Cheon[4], Young Seok Kim[1], Hong Soo Kim[3], Sang Gyune Kim[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea; [2]Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea; [3]Department of Internal Medicine, Soonchunhyang University Chunan Hospital, Chunan, Korea; [4]Department of Internal Medicine, Gangneung Asan Hospital, Gangneung, Korea

Aims: The purpose of this study is to find out whether spleen stiffness measurement (SSM) can predict the varices need treatment (VNT), and how it correlates with hepatic venous pressure gradient (HVPG) in patients with liver cirrhosis. Also, the newly announced Baveno VII criteria and other non-invasive tests (NITs) were validated.

Methods: Three hundred forty consecutive patients with liver cirrhosis who have undergone SSM and endoscopy were enrolled. SSM was done by Fibroscan® 630 Expert device (SSM@100Hz).

Results: The success rate of SSM was 94.71%, and factors related with SSM failure were high BMI (OR 1.53, 95% CI 1.16-2.02), small spleen volume (OR 0.86, 95% CI 0.81-0.92). The cut-off of SSM for predicting VNT was 38.25 *kPa*, showed high accuracy of AUC 0.91 (sensitivity 0.80, specificity 0.93, accuracy 0.86), and showed good results in both viral (AUC 0.93) and non-viral etiology (AUC 0.89). Also, SSM has higher prediction accuracy than other NITs including liver stiffness measurement (LSM). HVPG and spleen stiffness showed a significant correlation, especially in HVPG less than 16 *mmHg*. The accuracy of the Baveno VII criterion using LSM and platelet for predicting VNTs was AUC 0.70 while our model based on spleen stiffness showed a good performance to predict VNR.

Conclusions: SSM can predict VNT better than any other existing NITs in liver cirrhosis patients, which was probably due to high correlation between SSM and HVPG. SSM can provide clinical help to avoid unnecessary endoscopy in these patients.

Keywords: Spleen, Portal hypertension, Cirrhosis, Varices

[NAFLD]

PE-189

The Role of Vitamin E in the Treatment of Non-Alcoholic Steatohepatitis (NASH)

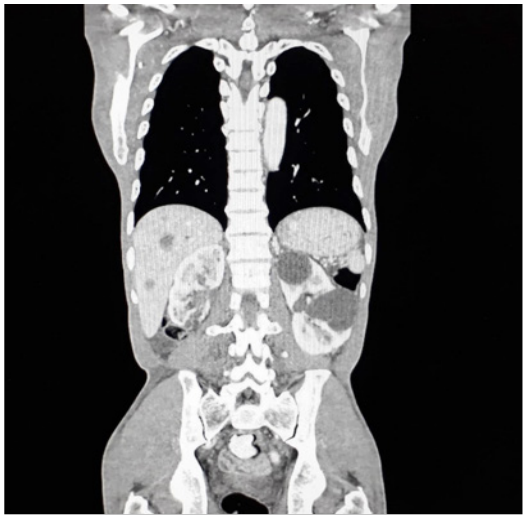
Mohamed Shafi Bin Mahboob Ali

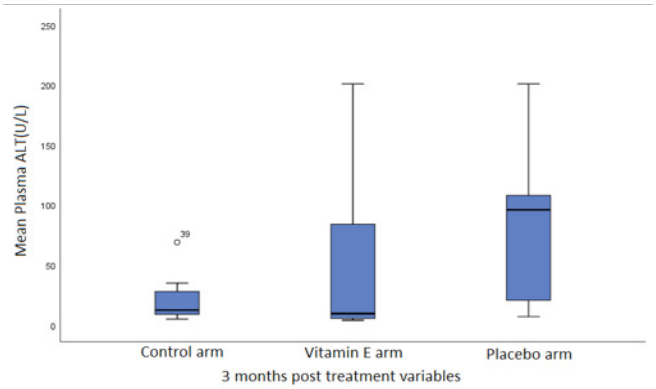
Advanced Medical and Dental Institute (AMDI), Malaysia

Aims: Oxidative stress plays a vital role in the transition from simple steatosis to nonalcoholic steatohepatitis (NASH). An effective therapeutic strategy is to target the reduction of oxidative stress in these patients. Vitamins with antioxidant properties have the ability to act through multiple mechanisms to decrease the levels of reactive oxygen species in the body and prevent oxidative damage in the cell that can lead to cellular senescence and apoptosis. These properties may halt the progression of liver injury and facilitate the reversal of hepatic fibrosis in patients with NAFLD who are at risk for developing NASH. Thus, the aim of this study is to explore the functions of vitamin E in the treatment and recovery of patients suffering from NASH in our centre.

Methods: About 60 patients that were non-diabetic and diagnosed with NASH based on cytology were recruited into the studies. The mean age of the subjects is 45 years old. Their Alanine Transaminase(ALT) level was recorded prior to segregation. The subjects were divided into two main arms in which one arm received 500IU of Vitamin E while the second arm received a placebo. They received these tablets on daily basis to be taken once a day and were asked to be recorded. After three months, their ALT levels were measured again and were compared between the two groups. A chi-square test was used to differentiate between the two variables. An Independent t-test was used to determine whether the variables were statistically significant. A scatter plot was plotted to demonstrate the direct correlation between the level of ALT and the duration of the patients who were on vitamin E.

Results: We found that the arm of subjects that received 500IU of vitamin E daily recorded a significant reduction of ALT levels compared to the placebo arm. The placebo arm showed no changes in their ALT level pre and post-administration of the placebo. We also found that there was a direct correlation between the duration of patients on vitamin E and the reduction of the ALT in the scatter plot. Any P values of <0.05 were taken as statistically significant.





Conclusions: Vitamin E at the dose of 500 IU/day is beneficial in non-diabetic adults with active NASH. Balancing the potential risks and benefits is vindicated before starting treatment while aggressive monitoring of cardiovascular disease complications should also be taken into consideration. Longer follow-up RCTs are needed to assess the long-term safety and therapeutic value of vitamin E on clinical outcomes in NASH patients. Assessment of vitamin E or antioxidant micronutrient status must also be emphasized. We can conclude from this study that consuming 500IU of vitamin E every day may improve hepatocyte injury and progressive hepatic damage, especially

in NASH by reducing the oxidative stress caused by the free oxygen radicals.

Keywords: Vitamin E, Anti-oxidant, Nonalcoholic steatohepatitis, Anti inflammatory

PE-190

Gut Microbiota and Leaky Gut in a High-Fat Diet-Induced NASH Animal Model

Sora Kirihara[1], Hinako Nakayama[1], Taketo Hukuoka[1], Koki Honma[1], Moe Fujii[3], Satoshi Hirohata[2], Shusei Yamamoto[1,2] Shogo Watanabe[2]

[1]Department of Medical Technology, Graduate School of Health Science, Okayama University, Japan, [2]Academic Field of Health Science, Okayama University, Japan, [3]Department of Medical Technology, Ehime Prefectural University of Health Sciences, Japan

Aims: Leaky gut is an increased intestinal permeability caused by disruption of the tight junction, an intercellular structure of the intestinal epithelium. In recent years, it has been reported that NASH is induced by imbalance of the intestinal microbiota due to excessive high-fat diets and the influx of pathogen-associated molecules (PAMPs), mainly lipopolysaccharides (LPS), from the intestinal tract through the portal vein to the liver. However, suitable animal models that can evaluate the relationship between non-alcoholic steatohepatitis (NASH) and leaky gut have not been established. In the present study, we investigated the gut microbiota and leaky gut in SHRSP5/Dmcr rats, which develops NASH induced by high fat and high cholesterol (HFC) diet.

Methods: 10 weeks male SHRSP5/Dmcr rats (n=10) and WKY/Izm rats (n=5) were divided into three groups: SHRSP5/Dmcr + normal diet (control group, n=5), WKY/Izm + +HFC diet (non-alcoholic fatty liver: NAFL group, n=5), and SHRSP5/Dmcr +HFC diet (NASH group, n=5).

Results: In the liver, lipid droplets were observed in the NAFL and NASH groups, and severe hepatic fibrosis was observed in the NASH group. Intestinal permeability by FITC-dextran testing was significantly high in the NAFL and NASH groups, and was more pronounced in the NASH group. In transmission electron microscopy (TEM), intestinal epithelial cells revealed tends to widen intercellular spaces and shorten microvilli in the NAFL and NASH groups. 16SrRNA analysis showed that Gram-negative bacteria producing LPS were increased in the NAFL and NASH groups. In addition, the Bacteroidetes phylum was increased in the NASH group.

Conclusions: NASH models fed HFC diet showed leaky gut syndrome. The HFC diet disrupted the tight junction and also changed gut microbiota. The excess production of LPS or PAMPs by dysbiosis may lead to NASH progression.

Keywords: Non-alcoholic steatohepatitis, Gut microbiota, Leaky gut, Lipopolysaccharides

PE-191

Cholesterol Crystals Aggravate NASH by Activating the NLRP3 Inflammasome

Hinako Nakayama[1], Sora Kirihara[1], Taketo Fukuoka[1], Koki Honma[1], Moe Fujii[3], Shusei Yamamoto[1,2], Satoshi Hirohata[2], Shogo Watanabe[2]

[1]Department of Medical Technology, Graduate School of Health Science, Okayama University, Japan, [2]Faculty of Health Science, Okayama University, Japan, [3]Department of Medical Technology, Ehime Prefectural University of Health Sciences, Japan

Aims: The inflammasome is a protein complex composed of multiple proteins, including the nucleotide-binding, oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3). It is activated by various stimuli such as pathogen-associated molecules like lipopolysaccharide (LPS) or cholesterol crystals etc.. Activated inflammasomes induce hepatitis by activating caspase-1 and maturating inflammatory cytokines such as IL-1β and IL-18, which may contribute to the pathogenesis of non-alcoholic steatohepatitis (NASH). In the present study, we examined how cholesterol accumulation in the liver exacerbates NASH via NLRP3 inflammasome.

Methods: SHRSP5/Dmcr rats were divided into two groups (CONT and NASH groups) and WKY/Izm rats were used as non-alcoholic fatty liver (NAFL) group. The NASH and NAFL groups were fed high-fat and high-cholesterol (HFC) diet for 8 weeks.

Results: The liver was enlarged and had an uneven surface in the NAFL and NASH groups compared to that in the CONT group, which was more pronounced in the NASH group. Severe hepatic fibrosis and lipid droplets were observed only in the NASH group. The NAFL group showed little or no fibrosis. In addition, inflammatory cytokine-related genes (TNF-α, NF-κB, IL-1β, and IL-18), endotoxin-related genes (TLR-4 and LBP), and inflammasome component genes (NLRP3 and Caspase-1) were upregulated in the liver of NASH group. Cholesterol crystals observed by polarizing microscope were particularly accumulated in the NASH group.

Conclusions: HFC diet caused accumulation of cholesterol crystals in NASH liver. Cholesterol crystals aggravate NASH by activating the NLRP3 inflammasome and upregulating the inflammatory cytokines such as IL-1β and IL-18.

Keywords: NASH, Cholesterol crystals, NLRP3 inflammasome, Lipopolysaccharide

PE-192

Uncommon Culprit of a Common Disease: A Case of a Drug Induced Steatohepatitis Secondary to Cyproterone Acetate, Ethinylestradiol

Magtoto, Edzel M., Adraneda, Celina Celeste H.

De Los Santos Medical Center- Department of Internal Medicine, Philippines

Aims: Drug-induced steatohepatitis (DISH) is one of the many varieties of Drug-Induced Liver Injury (DILI). DISH is commonly perplexed with NASH or NAFLD. The only way to classify DISH can only be identified via liver biopsy. Moreover, it is often difficult to monitor disease advancement of DISH, hence, use of non-invasive biomarkers is conclusive in the management and discontinuance of its progression.

This is a case of a 28-year-old female diagnosed case of Polycystic Ovarian Syndrome currently maintained with Cytoproterone acetate, Ethinylestradiol, an oral contraceptive pill. After thorough monitoring, patient was noted to have a recorded elevation of liver enzymes on her regular check-up. Patient was subjected for an Ultrasound

Guided Liver Biopsy which yielded Severe Steatohepatitis.

Methods: Over the preceding decades, many drugs have been categorized as theoretically harmful and can induce liver injury. These can lead to steatohepatitis especially in predisposed individuals. Amiodarone, methotrexate, tamoxifen, valproic acid, and glucocorticoids are some of the examples. Furthermore, drugs like steroid hormones can deepen the pathogenetic mechanisms which cause Non-alcoholic steatohepatitis (NASH) and or Non-alcoholic fatty liver disease (NAFLD).

Drug induced liver injury (DILI) is one of the frequent causes of acute liver failure and transplantation in Western countries. Due to its variable nature and possibly lethal course, it poses a severe clinical problem. Liver injury can develop following the use of many drugs. DILI accounts for an estimated ten percent (10%) in all cases of acute hepatitis while fifty percent (50%) in new onset jaundice patients. According to recent studies, DILI represents thirty-two percent (32%) of the causes of drug withdrawal.

There are several risk factors associated with the development of DILI. Adults and females generally have higher risk of acquiring DILI. Furthermore, drug-drug interactions cause hepatotoxicity. The most common drug induced DILI in the US is the use of Acetaminophen drug.

The diagnosis of DILI is challenging in several ways including the patient's history and clinical presentation. The typical acute presentations of drug induced liver injury are asymptomatic mild liver enzyme elevation with or without jaundice with a noted pattern which could be cholestatic, hepatocellular, or mixed. Symptoms of patients with acute DILI may progress to malaise, low grade fever, anorexia, nausea, vomiting, right upper quadrant pain, acholic stools, or even dark urine. Some patients may develop pruritus. Hepatomegaly can also be noted on physical examination. Severe cases would have coagulopathy and hepatic encephalopathy. Patients with chronic DILI may advance to fibrosis, cirrhosis, or hepatic decompensation.

DILI generally develops around six months from a newly introduced medication. Recently, studies showed that the use of herbal medication causes acute liver failure. Patients with an auto-immune like presentation may have serologic markers of autoimmunity such as elevation of ANA.

The pattern of injury can be helpful in the verdict of DILI. DILI with cholestasis is defined as an elevated ALP >2 times the upper limit of normal and or alanine transferase (ALT) to ALP ratio </2. Injury is regarded if the R value is greater than 2 but less than 5 while hepatocellular if the R value is >/5.

Identifying the offending drug is imperative. It is challenging due to the consistency in the drug history and patient's compliance. Even with a noted reliable drug history, the exposure to drug is not very clear.

Liver biopsy is not generally required to establish the diagnosis of DILI. However, histologic findings may be useful in understanding the etiology of liver injury and may rule out other causes.

Results: This is a case of a 28-year-old female, diagnosed with PCOS since 2016, on maintenance with Cyproterone acetate, Ethinylestradiol (Cyebelle) 2mg/45mcg 1 tab OD and was noted to be compliant.

On her regular follow up with her Attending Physician, for the mentioned morbidity, patient underwent several blood works which revealed significant elevation of liver enzymes.

AST OF 129 (3.79X), ALT 134 (2.43x), ALP 37, LDH 210 TBIL 0.61 B1 0.22 B2 0.39

Patient denies abdominal pain, nausea, vomiting, tea colored urine, acholic stools, jaundice, itchiness, headache, bleeding, and easy fatigability. Due to elevated liver enzymes, patient was then referred to GI service.

GI service ordered further blood work-ups as follows:

CBC Hgb 134 Hct 0.43 WBC 7.46, Neut 55 Lymph 39, Mono 5, Eos 1, Plt 399,

PT 11.4 v 11.9, % Act 99.7 INR 1.01,

TP 63.7, Alb 48 Alb 3.06

FT3 3.5 FT4 1.01 TSH 1.10.

Hepa profile was noted to be insignificant.

Whole Abdominal Ultrasound (6/25) revealed Hepatic Steatosis, right adrenal cysts likely ovarian, unremarkable sonogram of the rest of the abdominal structure, postvoid residues 5%, and prevoid 10%.

Gastro service ordered to discontinue Cybelle medications (last intake noted was June) and recommended repeat laboratories monthly.

During the interim, the patient denied any subjective complaints. Patient sought consult with AMD with repeat labs revealing:

8/27 AST 140 ALT 178 ALP 51 ANA (+) 1:40 speckled pattern

9/3 AST 184 AKT 182 ALP 62 TB 0.67 DB 0.35 B2 0.32 GGT 52 TP 7.56 Alb 4.7 Glob 2.86 A/G ratio1.64, PT 11.4 v 11.5, % Act 91.7% INR 1.05

In the interim, the patient remains to be asymptomatic with no noted subjective complaints. Due to persistence of the elevated liver enzymes, and recent lab workups, GI advised to undergo liver biopsy and was subsequently admitted. Patient was able to tolerate procedure with no noted untoward event.

The patient was stable and discharged while waiting for the Biopsy findings. Patient was prescribed with Omeprazole 40 mg tablet, 30 minutes before breakfast for 14 days, and Tramadol + Paracetamol 325/37.5 mg tab every 8 hours as needed for pain.

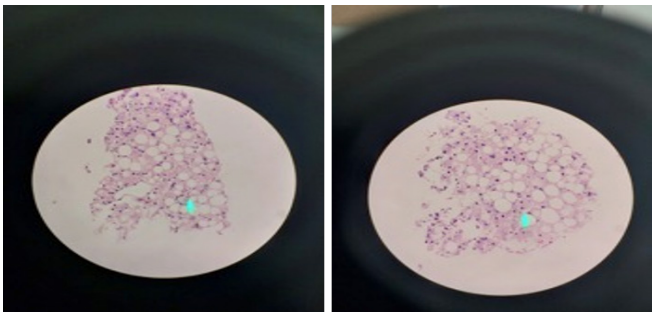
Conclusions: Cyproterone is a steroidal antiandrogen that has been used in the treatment of prostate cancer in many countries of the world. Cyropreterone is a derivate of hydroxyprogesterone and its mechanism of action is to block androgen receptor. It has been evaluated as a hormonally sensitive including Endometriosis, precocious puberty and infertility. It has been noted that Cyproterone is potentially hepatotoxic with noted inferior efficacy when compared to other antiandrogens.

Drug induced liver injury (DILI) and herbal induced liver injury (HILI) are problems known to mimic both acute and chronic liver diseases. Steatosis and steatohepatitis are rare but well documented types. DIS/DISH may present as macro vesicular steatosis, micro vesicular steatosis, or steatohepatitis, depending on the mechanism of a specific lipotoxic drug, which may show variable latency prior to the occurrence of a clinically apparent injury.

The diagnosis of DIS/DISH remains to be of high index of suspicion since it is still a rare cause of steatosis. Liver biopsy remains the gold standard for the diagnosis of NAFLD. We have facilitated Ultrasonography as the recommended first line imaging technique which is a non-invasive method to identify presence of fibrosis. Ultrasound guided liver biopsy was performed on the patient.

Using mononuclear cells, neutrophils, eosinophils and lymphocytes or cholestasis, the tiver histology shows apoptosis, necrosis and inflammatory infiltrates. The liver core biopsy was noted to have severe steatosis, and mild portal and lobular chronic inflammation without fibrosis. A correlation with serologic markers were facilitated as recommended for final interpretation. The autoimmune test performed

on the patient showed ANA positive while the IgG Ama, Agm, ASMA, Anti Lkm-1 were all negative.



Diverse drugs have been associated with DILI and it is expected to continuously increase due to medical approval and new onset molecules including the improved knowledge of physicians and patients pertaining to this health issue. Close monitoring of liver function and proper identification of clinical signs and symptoms are imperative to the perception of the use of drugs with potential hepatotoxic properties resulted to incidence of DILI.

Keywords: Drug induced liver injury, Steatohepatitis, Steatosis

PE-193

Association of NAFLD with COVID-19 Outcomes: A Meta-Analysis

Ruby Singh

Independent Researcher, Delhi, India

Aims: COVID-19 prevalence is higher among NAFLD patients, and they also experience worse clinical outcomes of the disease, including higher mortality rates, disease severity, and intensive care unit (ICU) admission rates. However, this evidence has not been thoroughly examined in the literature. To address this gap, this meta-analysis aims to compare the clinical outcomes of COVID-19 between NAFLD patients and those without NAFLD.

Methods: The search for relevant studies was conducted in MEDLINE, EMBASE, and Cochrane Central databases, covering the period from inception through November 2022. The inclusion criteria were epidemiological studies that evaluated clinical outcomes in COVID-19 patients with NAFLD. The quality of the studies was assessed using the Newcastle-Ottawa Scale. The RevMan was used to calculate the pooled estimates using the random-effects model.

Results: This study included 16 observational studies, including 1846 NAFLD patients. The studies included in the meta-analysis exhibited significant heterogeneity, and their quality ranged from moderate to high, with a mean quality score of 8 (range: 6 to 8). NAFLD was associated with an increased risk of severe COVID-19 among NAFLD patients [OR=2.60; p<0.001]. The OR for ICU admission due to COVID-19 was 1.64 (p<0.001). However, there was no significant association between NAFLD and COVID-19-associated mortality (OR=1.03; p=0.93).

Conclusions: This study found NAFLD patients had a higher risk of severe COVID-19 and ICU admission compared to non-NAFLD patients, but there was no significant difference in mortality between the two groups.

Keywords: NAFLD, COVID, Hospitalization, Meta-analysis

PE-194

Untangling the Role of Proinflammatory Cytokines in T2DM Patients with Non-Alcoholic Fatty Liver Disease

Rajiv Nehra

Department of Biochemistry, RD Medical College, Banda, U.P, India

Aims: Type 2 diabetes mellitus (T2DM) is associated with chronic inflammation and oxidative stress, implicated in the pathophysiology of non-alcoholic fatty liver disease. Oxidative stress plays an important role in the development of vascular complications in type 2 diabetes. Oxidant derived tissue injury occurs when production of oxidants or reactive oxygen species (ROS) exceeds local antioxidant capacity. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin (IL-6) and various growth factors in hepatic cells modulate the local response are responsible for liver injury.

Methods: 10 ml of fasting venous blood was collected from the anticubital vein in a plain, fluoride and EDTA vacutainers. The blood sample was centrifuged and stored at 4^0 C for biochemical and immunological investigations. The study group consisted of n=50 healthy individuals (Group I), n=25 Type II Diabetic without NAFLD (Group II), n=25 Type II diabetic with NAFLD (Group III) of either sex aged between 50-65 years. The diagnosis of NAFLD was done by ultrasonographic examination of liver. Serum levels of inflammatory markers (IL-6 & TNF-a), antioxidants (Glutathione reductase), plasma malondialdehyde (MDA), hs-CRP were estimated.

Results: Concentration of inflammatory molecules such as TNF-a 9.32±1.08, 14.04±1.42 and 36.56±10.50; IL-6 9.24±1.20, 14.14±1.50 and 36.76±11.56; hs-CRP 0.90±1.10, 1.96±0.50 and 2.18±0.90 was significantly elevated in Group III. GSH were significantly lower in both the groups of Diabetic with and without NAFLD when compared to controls. 7.10±0.58, 6.90±0.70 and 5.80±0.80. Mean value of total MDA 2.32±0.98, 8.68±2.50 and 9.80±2.72 was significantly more in Group III as compared to Group I and Group II.

TABLE I- BIOCHEMICAL PARAMETERS IN NORMAL, T2DM WITHOUT NAFLD AND T2DM WITH NAFLD

INDIVIDUALS	FBS (mg/dl)	HbA1c (%)	Total Bilirubin (mg/dl)	Total Protein (gm/dl)	Albumin (gm/dl)	SGPT (IU/L)	ALP (IU/L)
Normal n=50 (Group I)	91.60±10.44	6.28 ± 1.42	00.72 ± 00.18	7.50±1.13	4.20 ± 1.00	27.34±06.44	179.7±36.75
T2DM without NAFLD n=25 (Group II)	180.88±20.54	8.98 ± 2.21	00.72 ± 00.26	8.10±1.32	4.40 ± 1.20	28.12±4.09	267.7±12.60
T2DM with NAFLD n=25 (Group III)	253.30±28.12**	11.00 ± 2.06**	01.07±00.29^{NS}	8.10±2.50**	4.50 ± 1.40**	60.07±9.80**	309.7±26.90**

The data were expressed as mean ± SD. The data was analyzed using the student's t- test. *indicates p<0.05 and statistically significant, **indicates p<0.001 and statistically highly significant

TABLE-I

With respect to biochemical parameters, the mean values of fasting blood sugar 91.60±10.44, 180.88±20.54 and 253.30±28.12.; HbA1c 6.28±1.42, 8.98±2.21 and 11.00±2.06 were significantly elevated in Group III compared to Groups I and II.

When liver function tests were compared between groups, Mean values of T.Bilirubin 00.72±00.18, 00.72±00.26 and 1.07±00.29; T.Protein 07.50±1.13, 8.10±1.32 and 8.10±2.50 and Albumin 4.20±1.00, 4.40±1.20 and 4.50±1.40; SGPT 27.34±06.44, 28.12±4.09 and 60.07±9.80 was significantly higher in Group III compared to Group I and II.

ALP 179.7±36.75, 267.7±12.60 and 309.7±26.90 was significantly increased in Group III when Compared to Group I and Group II.

TABLE II- INFLAMMATORY AND OXIDATIVE STRESS LEVEL IN NORMAL, T2DM WITH NAFLD AND T2DM WITHOUT NAFLD

INDIVIDUALS	TNF-α (pg/ml)	IL-6 (pg/ml)	GSH (mg/dl)	MDA (µmol/L)	hs-CRP (mg/L)
Normal n=50 (Group I)	9.32±1.08	9.24±1.20	7.10±0.58	2.32±0.98	0.90±1.10
T2DM without NAFLD n=25 (Group II)	14.04±1.42*	14.14±1.50*	6.90±0.70	8.68±2.50	1.96±0.50*
T2DM with NAFLD n=25 (Group III)	36.56±10.50**	36.76±11.56**	5.80±0.80*	9.80±2.72**	2.18±0.90*

The data were expressed as mean ± SD. The data was analyzed using the student's t-test. * indicates p<0.05 and statistically significant, **indicates p<0.001 and statistically highly significant

TABLE-II

Concentration of inflammatory molecules such as TNF-α 9.32±1.08, 14.04±1.42 and 36.56±10.50; IL-6 9.24±1.20, 14.14±1.50 and 36.76±11.56; hs-CRP 0.90±1.10, 1.96±0.50 and 2.18±0.90 was significantly elevated in Group III.

GSH were significantly lower in both the groups of T2DM with and without NAFLD when compared to controls. 7.10±0.58, 6.90±0.70 and 5.80±0.80 (Table II). Diabetes as a risk factor for NAFLD is closely associated with increased oxidative stress, and the duration of diabetes plays an important role in increasing the level of oxidative damage and reducing antioxidant defense.

Mean value of total MDA 2.32±0.98, 8.68±2.50 and 9.80±2.72 was more in Group III compared to Groups I & II with a significant p value.

Results of the present study indicates that inflammatory markers and oxidative stress are increased with decreased antioxidant defense levels in patients with T2DM due to hyperglycemia induced oxidative stress.

Conclusions: Results of the present study indicates that inflammatory markers and oxidative stress are increased with decreased antioxidant defense levels in patients with NAFLD in T2DM.

Keywords: T2DM, NAFLD, Cytokines, MDA

PE-195

Response of Mediators of Inflammation in Liver NAFLD

Manju Rani

CHC, Siyana, Bulandshehar, U.P, India

Aims: Acute phase proteins are synthesized predominantly in the liver with all hepatocytes possessing the capacity to produce the entire spectrum of these proteins in response to tissue injury as a result of neoplasia, trauma and infection. The various APP differ markedly in the rise or decline of their plasma levels and also in their final concentrations. APP generates a characteristic serum protein profile. There are many diseases in which the rise in the synthesis of acute phase proteins parallels the degree and progression of the inflammatory processes. CRP, the major acute phase reactants in humans, derives mainly from hepatocytes in response to IL - 6 and is then secreted into the systemic circulation.

Methods: 10 ml of fasting venous blood was collected from the anticubital vein in a plain, fluoride and EDTA vacutainers. The blood sample was centrifuged and stored at 4^0 C for biochemical and immunological investigations. The study group consisted of n=50 healthy individuals (Group I), n=25 AFLD (Group II), n=25 NAFLD (Group III) of either sex aged between 50-65 years. The diagnosis of Liver disease was done by ultrasonographic examination of liver. Serum levels of cytokine (IL-6) and acute phase protein (hs-CRP) were estimated.

Results: Concentration of cytokine IL-6 9.24±1.20, 36.76±11.56 and 14.14±1.50; acute phase protein hs-CRP 0.90±1.10, 2.18±0.90 and 1.96±0.50 was significantly elevated in Group II as compared to Group I and Group III.

Conclusions: Results of the present study indicates that the levels of CRP and IL-6 increased in parallel with the progression of chronic liver diseases.

Keywords: Liver, NAFLD, CRP, IL6

Table-I APP and CYTOKINE LEVEL IN NORMAL, AFLD AND NAFLD

INDIVIDUALS	IL-6 (pg/ml)	hs-CRP (mg/L)
Normal n=50 (Group I)	9.24±1.20	0.90±1.10
AFLD n=25 (Group II)	36.76±11.56**	2.18±0.90*
NAFLD n=25 (Group III)	14.14±1.50*	1.96±0.50*

The data were expressed as mean ± SD. The data was analyzed using the student's t-test. * indicates p<0.05 and statistically significant, **indicates p<0.001 and statistically highly significant

Concentration of Cytokine such as IL-6 : 9.24±1.20, 36.76±11.56 and 14.14±1.50; and APP like hs-CRP 0.90±1.10, 2.18±0.90 and 1.96±0.50 was significantly elevated in Group II.

TABLE II- BIOCHEMICAL PARAMETERS IN NORMAL, T2DM WITHOUT NAFLD AND T2DM WITH NAFLD

INDIVIDUALS	FBS (mg/dl)	HbA1c (%)	Total Bilirubin (mg/dl)	Total Protein (gm/dl)	Albumin (gm/dl)	SGPT (IU/L)	ALP (IU/L)
Normal n=50 (Group I)	91.60±10.44	6.28 ± 1.42	00.72 ± 00.18	7.50±1.13	4.20 ± 1.00	27.34±06.44	179.7±36.75
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T2DM with NAFLD n=25 (Group III)	253.30±28.12**	11.00 ± 2.06**	01.07±00.29^{NS}	8.10±2.50**	4.50 ± 1.40**	60.07±9.80**	309.7±26.90**

The data were expressed as mean ± SD. The data was analyzed using the student's t- test. *indicates p<0.05 and statistically significant, **indicates p<0.001 and statistically highly significant

TABLE-II

With respect to biochemical parameters, the mean values of fasting blood sugar 91.60±10.44, 180.88±20.54 and 253.30±28.12.; HbA1c 6.28±1.42, 8.98±2.21 and 11.00±2.06 were significantly elevated in Group III compared to Groups I and II.

When liver function tests were compared between groups, Mean values of T.Bilirubin 00.72±00.18, 00.72±00.26 and 1.07±00.29; T.Protein 07.50±1.13, 8.10±1.32 and 8.10±2.50 and Albumin 4.20±1.00, 4.40±1.20 and 4.50±1.40; SGPT 27.34±06.44, 28.12±4.09 and 60.07±9.80 was significantly higher in Group III compared to Group I and II.

ALP 179.7±36.75, 267.7±12.60 and 309.7±26.90 was significantly increased in Group III when Compared to Group I and Group II.

PE-196

The Clinical Usefulness of the Visceral Fat Thickness Measured by Abdominal Ultrasonography in Patients with Non-Alcoholic Fatty Liver Disease

Young Chang[1], Soung Won Jeong[1]*, Jae Young Jang[1], Sae Hwan Lee[2], Jeong-Ju Yoo[3], Sang Gyune Kim[3], Young Seok Kim[3], Hong Soo Kim[2]

[1]Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan, Korea, [3]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Korea, [4]Department of Pathology, Soonchunhyang University College of Medicine, Seoul, Korea

Aims: Insulin resistance and metabolic syndrome are complex conditions that involve a combination of genetic, lifestyle, and environmental factors. They are typically diagnosed using a combination of clinical criteria, blood tests, and physical examinations. This study was aimed to predict insulin resistance and metabolic syndrome simply using abdominal ultrasonography measurements.

Methods: This single-center prospective study involved 86 patients diagnosed as fatty liver by ultrasound from November 2019 to December 2020. The correlations between the measurements of visceral obesity by abdominal ultrasound and metabolic syndrome and insulin resistance were analyzed using Pearson's correlation test and logistic regression. The receive operating characteristic (ROC) curve was used to analyze the sensitivity and specificity of abdominal ultrasound measurements as a predictive index for metabolic syndrome and insulin resistance.

Results: Among the measures of visceral fat at various angles, the vertical distance from the navel to the aorta (Pearson correlation=0.37; p=0.0004) and the horizontal distance from the flank to the spine (Pearson correlation=0.34; p=0.0009) were significantly associated with homeostatic model assessment for insulin resistance (HOMA-IR). In metabolic syndrome, the vertical distance from the navel to the aorta (Pearson correlation=0.32; p=0.005) and the horizontal distance from the flank to the spine (Pearson correlation=0.33; p=0.003) showed a significant correlation. The combination of vertical distance from the navel to the aorta and the horizontal distance from the flank to the spine predicted metabolic syndrome and insulin resistance well with area under the ROC curve (AUROC) of 0.720 and 0.797. When the fatty liver grade measured by ultrasound was added to the model, the predictive power for metabolic syndrome and insulin resistance increased to AUROC of 0.775 and 0.803, respectively.

Conclusions: Metabolic syndrome and insulin resistance can be easily predicted by measuring visceral fat and evaluating fatty liver with ultrasound. (KCT007868)

Keywords: Ultrasonography, Fatty liver, Metabolic syndrome, Insulin resistance

PE-197

Liver Disease Treatment Effect of Metformin and Empagliflozin Combination in NASH Model

Mi Ra Lee, Jin Suk Lee, Seul Ki Han, Soon Koo Baik, Moon Young Kim*

Department of Internal Medicine, Wonju Severance Christian Hospital, Regeneration Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea

Aims: Although the prevalence of fatty liver and its complications are increasing, treatment drugs are lacking. Therefore, we wanted to explore the effects of metformin and empagliflozin, currently used diabetes treatments, as a treatment for fatty liver.

Methods: For *in vivo* experiments, a high fat (45% of cholesterol contained)-TAA injection (300 mg/kg, twice a week/8 weeks, IP) model was created using C57BL/6 (8 weeks, 20-25g), Empagliflozin (10 mg/kg/day) and metformin (100 mg/kg/day) were administered. For *in vitro* experiments, LX2 cells were treated with TGF-β (5ng/ml) and then empagliflozin (100 uM) and metformin (20 mM) were administered. RAW 264.7 cells were treated with IFNg+LPS and then empagliflozin (400 uM) and metformin (20 mM) were administered. Expression patterns of markers related to inflammation and fibrosis (α-SMA, type I collagen, TNF-α, IL-1β, IL-6, iNOS, etc.) were comparatively analyzed through qPCR and western blot.

Results: TNF-alpha, which increased in the fatty liver-fibrosis group, was decreased when metformin and empagliflozin were treated, respectively, but there was no synergetic effect. There was no difference in iNOS between the control group and the fatty liver-fibrosis group, but it decreased in all of the drug-treated groups. When metformin and empagliflozin were treated in LX-2 cells activated with TGF-beta1, alpha-SMA was decreased at the RNA and protein level, and Collagen I was decreased by metformin at the protein level, and further decreased when treated with empagliflozin. When RAW 264.7 cells activated with IFNg+LPS were treated with metformin and empagliflozin for 24 and 48 hours, the expression levels of TNF-α, IL-1β, IL-6, and iNOS related to inflammation were all decreased in the drug-treated group, and a synergetic effect was also observed.

Conclusions: It is expected that this will be an opportunity to expand the treatment options for fatty liver patients by preparing evidence to confirm the treatment effects of diabetes drugs that are already widely used, and to provide prescription options for diabetes drugs to patients with liver cirrhosis.

Keywords: Inflammation, Fibrosis, Empagliflozin, Metformin, NASH

PE-198

Chemotherapy Induced Fatty Liver in Ovarian Cancer

Harshita Dubey, Amar Ranjan, Pranay Tanwar

All India Institute of Medical Sciences, New Delhi, India

Aims: Chemotherapy induced liver injury is one of the common causes of mortality in cancer patient. One of the mechanisms of development of fatty liver is hepatic steatosis induced by chemotherapeutic agents. Here in this study we are evaluating the development of fatty liver during the therapy for ovarian cancer.

Methods: A prospective study was conducted on cases of ovarian cancer with normal liver function test, which developed fatty liver after getting chemotherapy.

Results: We studied 200 cases of ovarian cancer, out of which 31 (15%) cases developed fatty liver secondary to therapy for ovarian cancer. The mean value of age that developed fatty liver is 49.2 years. Among various clinical parameters, only weight and body surface area (BSA) did show a statistically significant correlation (p=0.05) with the development of fatty liver. The patients who had PFI more than 15 months also showed the development of FL (p=0.03) (table 1).

Conclusions: Development of fatty liver following chemotherapy follows the common mechanism, but the process is fast. This may be due to an altered metabolic process. Here also weight and BSA are associated with the development of fatty liver. Following chemotherapy, progression-free interval also has shown a significant correlation with the development of fatty liver.

Keywords: Fatty liver, Ovarian cancer, Chemotherapy

Table 1: A statistical correlation between the developments of fatty liver with different clinical parameters (Point-Biserial Correlation)

		FL (N=31)		
	Mean values	N	Correlation coefficient	P-value
Age	49.2±7.95	31	0.04083397	0.5089
Height	151±8.2	30	-0.02402475	0.7565
Weight	59.37±13.93	31	0.1501248	0.0521
BSA	1.56±0.2	30	0.1533173	0.05292
CA125	68848.6±110251.5	18	0.08643838	0.2786
HE4	452.28±564.22	11	0.02149196	0.812
CA19.9	61.12±129.62	21	-0.01088773	0.8955
CEA	1.8±1.13	21	-0.05292008	0.5159
GFR	88.4±24.9	18	-0.04770862	0.6608
Tumor Size	11.77±6.6	24	-0.03569661	0.652
FCB	18.36±7.32	19	-0.1035075	0.2586
LCB	26.5±11.2	17	-0.01796504	0.8515
Menarche	13.6±1.1	10	0.05972043	0.6392
Menopause	45.7±5	22	0.04035766	0.6227
PFI	15.4±12.2	5	0.3778583	0.03016

PE-199

Clinical Implication of Hepatitis B Virus Infection with Non-Alcoholic Fatty Liver Disease in Primary Care Institution

Min Seong Kim

Millenium Seoul IM Clinic

Aims: Chronic hepatitis B (CHB) is prevalent among a significant proportion of patients in Korea and Asia. When patients with hepatitis B visit primary medical institutions, they typically undergo DNA and blood iron tests, as well as liver function tests. Consequently, it is crucial to investigate a cohort of CHB patients with non-alcoholic fatty liver disease (NAFLD) in order to determine their specific clinical characteristics.

Methods: Between April 2020 and December 2022, CHB patients undergoing follow-up examinations at Millennium Seoul Internal Medicine were included in the study. Information regarding underlying diseases, liver function tests, and ultrasonography results were collected. A case-control study design was employed to assess potential risk factors associated with NAFLD, including diabetes, hypertension, height, weight, among others.

Results: The study included a total of 65 adult patients with CHB, with a mean age of 45.2 years. 19 cases were found to have fatty liver upon ultrasound examination. Overweight and obese CHB patients exhibited an elevated risk of developing NAFLD compared to individuals with a normal weight. (89.4%(17/19) vs 21.9%(10/46), p<0.005) The incidence of fatty liver was significantly associated with the presence of co-occurring type 2 diabetes (DM).(15.9%(3/19) vs 6.5%(3/46), p=0.457) However, no confirmed association was found between viral factors and the incidence of NAFLD. Significant interaction between body mass index and sex was observed regarding the occurrence of NAFLD.

Conclusions: The findings of this study highlight the crucial role of weight and the presence of diabetes among patients with hepatitis B. Further extensive research is warranted to deepen our understanding of this relationship.

Keywords: HBsAg, NAFLD, DM, BMI

PE-200

Effects of Simvastatin Administration on the Severity of Steatosis in the Liver of Wistar Rats Induced by Dyslipidemia

Adi Nugraha[1], Miranti Dewi Pramaningtyas[2], Ety Sari Handayani[3], Dewa Nyoman Murti Adyaksa[4]

[1]Faculty of Medicine, Universitas Islam Indonesia, Sleman, Yogyakarta, Indonesia, [2]Department of Physiology, Faculty of Medicine, Universitas Islam Indonesia, Sleman, Yogyakarta, Indonesia, [3]Department of Anatomy, Faculty of Medicine, Universitas Islam Indonesia, Sleman, Yogyakarta, Indonesia, [4]Department of Anatomical Pathology, Faculty of Medicine, Universitas Gadjah Mada, Sleman, Yogyakarta, Indonesia

Aims: This research aimed to determine the effect of *simvastatin* on the severity of steatosis in the liver of Wistar rats induced by dyslipidemia.

Methods: This research consisted of 14 rats that divided into two groups: the first group (A) induced dyslipidemia and the second group (B) induced dyslipidemia plus simvastatin 0.18 mg/200g BW. Induction of dyslipidemia was carried out with egg yolk and propylthiouracil (PTU) via oral gavage for six weeks. The severity of steatosis was determined based on histopathological observations. The histopathology overview used a hematoxylin-eosin (HE) method for coloring. Fisher's exact test was used to analyze the obtained data.

Results: The first group had two preparations with mild steatosis degrees and four preparations with moderate steatosis. The second group had four preparations with mild degrees of steatosis and three preparations with moderate degrees of steatosis. One rat was dead during the treatment and not included in the analysis. The results of Fisher's exact test showed that there was no significant difference in severity between the treatment groups (p=0.592).

Conclusions: There was no significant difference between each group in the severity of steatosis in the liver of Wistar rats induced by dyslipidemia.

Keywords: Simvastatin, Steatosis, NAFLD, Dyslipidemia

PE-201

Discovery Biomarker to Optimize Obeticholic Acid Treatment for Non-Alcoholic Fatty Liver Disease

Seung Min Lee[1], Dae Won Jun[1,2*], Eileen Laurel Yoon[2*], Ju Hee Oh[1], Yoon Jin Roh[3], Eun Jeoung Lee[1], Ji-Hee Shin[4], Young-Do Nam[4], Hyun Sung Kim[5]

[1]Department of Translational Medicine, Graduate School of Biomedical Science & Engineering, Hanyang University, Seoul, Republic of Korea, [2]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea, [3]Department of Dermatology, Chung-Ang University Hospital, Seoul, Republic of Korea, [4]Research Group of Healthcare, Korea Food Research Institute, Jeon Ju, Korea, [5]Pathology, Medical genetic, Hanyang University College of Medicine, Seoul, Republic of Korea

Aims: Though obeticholic acid (OCA) is a promising drug for non-alcoholic fatty liver disease (NAFLD), the response rate of OCA is limited. This study aimed to develop a biomarker to optimize OCA treatment for NAFLD.

Methods: C57BL/6N mice males were fed on a western diet for 24 weeks. Pre-study liver biopsy performed at 12 weeks, and stratified according to disease severity. Next, the mice were administered with OCA (5 mg/kg/day) or vehicle for additional eight weeks. Hepatic transcriptome, metabolome and intestinal microbiome analyses compared according to OCA treatment responder and non-responder using pre-study and end of study samples. LX-2 cells transfected with short-interfering RNA against *CYP7B1* (siCYP7B1) and/or treated with OCA to evaluate the role of CYP7B1 in NAFLD.

Results: Resolution rate of steatohepatitis in the OCA and vehicle groups were 36.8% and 0%, respectively. The hepatic transcriptome and bile acid metabolite profile analyses revealed that the alternative bile acid synthesis pathway (Cyp7b1 and muricholic acid) in the OCA-responder group were upregulated compared with those in the OCA-non-responder group. Intestinal microbiome analysis also revealed that the abundances of *Bacteroidaceae*, *Parabacteroides*, and *Bacteroides*, which were positively correlated with the alternative bile acid synthesis pathway, were higher in the OCA-responder group than in the non-responder group. Pre-study hepatic mRNA levels of *Cyp8b1* (classic pathway) were downregulated in the OCA-responder group. The OCA response rate increased up to 80% in cases with a hepatic Cyp7b1/Cyp8b1 ratio ≥ 5.0. CYP7B1 expression was regulated by glucose concentration, and anti-fibrotic effect of OCA showed CYP7B1 dependent manner.

Conclusions: The upregulated alternative bile acid synthesis pathway or high hepatic CYP7B1 can be a potential biomarker for predicting OCA response.

Keywords: Obeticholic acid, Nonalcoholic fatty liver, Biomarker

PE-202

Synergistic Effect of Hepatic Steatosis and Diabetes Mellitus on Significant Liver Fibrosis

Won Sohn, Yong Kyun Cho, Byung Ik Kim

Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: This study aimed to investigate the risk factors for significant fibrosis in patients according to the presence of diabetes and fatty liver.

Methods: A cross-sectional study was conducted based on a cohort from a health examination program which included magnetic resonance elastography (MRE). We classified four groups according to diabetes mellitus and fatty liver: Group 1, no diabetes without fatty liver; Group 2, no diabetes with fatty liver; Group 3, diabetes without fatty liver; Group 4, diabetes with fatty liver. Fatty liver was evaluated by ultrasonography. Significant fibrosis was defined as liver stiffness measurement (LSM) ≥2.97 kPa on MRE. We evaluated the difference in significant fibrosis by four groups and analyzed the risk factors for significant fibrosis after adjusting for confounding factors.

Results: A total of 1,899 subjects were included. The number of Group 1, Group 2, Group 3, and Group 4 was 902 (47%), 796 (42%), 47 (3%), and 154 (8%), respectively. Mean values of LSM in Group 1, 2, 3, and 4 were 2.34±0.31 kPa, 2.42±0.37 kPa, 2.49±0.51 kPa, and 2.66±0.70 kPa, respectively (p<0.001). There was a significant difference in significant fibrosis (≥2.97 kPa) between four groups: 2.3%, 3.6%, 6.4%, and 19.5% in Group 1, 2, 3, and 4, respectively (p<0.001). The multivariable-adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for significant fibrosis comparing Group 4, Group 3, and Group 2 to Group 1 were 4.35 (2.14–8.85), 2.43 (0.65–9.12), and 0.96 (0.50–1.85), respectively (p<0.001, p=0.197, and p=0.907).

Conclusions: The risk of significant fibrosis is high in patients with diabetes and fatty liver rather than those who have one of each. Although all patients with fatty liver have the risk of hepatic fibrosis, it is needed to assess and manage hepatic fibrosis in patients accompanied by diabetes in particular.

Keywords: Nonalcoholic fatty liver disease, Liver fibrosis, Diabetes

PE-203

Risk Factors for Significant Fibrosis in Non-Obese Asian Patients with Non-Alcoholic Fatty Liver Diseease

Hyo Young Lee[1], Won Sohn[2], Yong Kyun Cho2, Byung Ik Kim[2]

[1]Division of Gastroenterology, Department of Internal Medicine, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, [2]Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: It is unclear which risk factors are associated with hepatic fibrosis in non-obese patients with non-alcoholic fatty liver disease (NAFLD). This study aimed to investigate the risk factors for significant liver fibrosis in in non-obese Asian patients with NAFLD including body mass index (BMI).

Methods: A cross-sectional study was conducted using nationally representative samples from the Korean National Health and Nutrition Examination Survey 2012-2019. A total of 1,200 Korean patients with NAFLD and BMI <25 kg/m^2 were enrolled in the study. NAFLD was defined as hepatic steatosis index ≥36. Liver fibrosis was assessed using Fibrosis-4 (FIB-4) index. The significant liver fibrosis was defined as FIB-4 index was more than 1.3. We classified into lean NAFLD (BMI <23 kg/m^2) and overweight NAFLD (BMI 23-25 kg/m^2). Univariable and multivariable logistic regression analyses were done to assess the risk factors including lean and overweight for significant liver fibrosis in patients with NAFLD.

Results: The mean age was 51 years and 47% (n=560) was male sex. The proportion of significant fibrosis was 14% (n=169). They consisted of 20% (n=236) of lean NAFLD and 80% (n=964) of overweight NAFLD. There was no difference in age and sex between two groups. However, the prevalence of hypertension and visceral obesity were higher in overweight NAFLD than in lean NAFLD (all p<0.05). A univariable analysis indicated that overweight NAFLD was associated with significant fibrosis compared to lean NAFLD (odds ratio [OR] 1.86 with 95% confidence interval [CI]: 1.15-3.00, p=0.012). However, a multivariable analysis showed that there was no difference in significant difference between two groups (OR 1.37 with 95% CI: 0.82-2.30, p=0.231). On the other hand, significant fibrosis was associated with other metabolic factors in the multivariable analysis: visceral obesity (OR 2.12 with 95% CI: 1.45-3.09, p<0.001), diabetes mellitus (OR 3.19 with 95% CI: 2.17-4.68, p<0.001), and hypertension (OR 2.91 with 95% CI: 2.01-4.22, p<0.001).

Conclusions: BMI is not a risk factor for significant fibrosis in non-

obese Asian patients with NAFLD. However, metabolic factors such as visceral obesity, diabetes, and hypertension are associated with liver fibrosis in non-obese Asian patients with NAFLD.

Keywords: Nonalcoholic fatty liver disease, Liver fibrosis, Obesity

PE-204

The Efficacy of N-Acetylcysteine for the Treatment of Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Preclinical Studies with Comprehensive Transcriptomic Analysis

Keungmo Yang[1,2], Hyun Yang[1,2], Si Hyun Bae[1,2], Chang Wook Kim[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [2]Division of Hepatology, Department of Internal medicine, College of Medicine, Eunpyeong St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea

Aims: The continuous rise in the prevalence of nonalcoholic fatty liver disease (NAFLD) and its comorbidities is emerging as a global health issue; however, there is no approved drug. Over the past decades, numerous studies have reported the protective effects of N-acetylcysteine (NAC), an antioxidant, against drug-induced liver injury. However, it is still unclear whether NAC has therapeutic potential in NAFLD. Therefore, the present meta-analysis aimed to investigate the efficacy of NAC on NAFLD in preclinical studies.

Methods: By searching PubMed, Web of Science, and Cochrane Library, a total of 13 studies were included. The methodological quality was assessed based on the SYstematic Review Centre for Laboratory animal Experimentation guideline, and heterogeneity was evaluated with *I2* and *P* values. Publication bias was assessed by Egger's test, and sensitivity analysis was performed.

Results: The results showed that NAC treatment significantly improved systemic and hepatic lipid metabolism ($p<0.01$), liver injury ($p<0.01$), glucose intolerance ($p<0.05$), and hepatic steatosis ($p<0.01$) by restoring hepatic levels of glutathione (GSH) ($p<0.05$) and GSH reductase ($p<0.05$) compared to controls in NAFLD-induced animals. However, the hepatic levels of GSH peroxidase, catalase, and superoxide dismutase were not changed by the administration of NAC in NAFLD-induced animals. Consistently, when we comprehensively analyzed bulk, single-cell, and spatial transcriptomics data, the above-mentioned target pathways of NAC were strongly associated with NAFLD development in mice and patients.

Conclusions: In summary, our findings suggest the possible application of NAC in future NAFLD clinical trials, either alone or in combination with other drugs.

Keywords: Nonalcoholic fatty liver disease, N-acetylcysteine, Meta-analysis, Lipid metabolism, Glutathione, Transcriptomics

PE-205

Association of Controlled Attenuation Parameter and Liver Stiffness with Coronary Heart Disease in Patients with Diabetes Mellitus

Hannah Lee, Oh Sang Kwon, Seung Kak Shin, Kiyoung Lee, Young Sil Eom, Byung-Joon Kim, Yun Soo Kim, Ju Hyun Kim

Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, South Korea

Aims: Accumulating evidence from various studies suggests risk of coronary heart disease is higher in patients with NAFLD. This study aimed to determine whether degree of steatosis and fibrosis are correlated with the risk of coronary heart disease (CHD) in patients with diabetes mellitus (DM).

Methods: A total of 324 patients with DM was enrolled between January and August 2022, after excluding viral hepatitis, cirrhosis, and any cancers. The body weight (BW), body mass index (BMI), waist circumference (WC), laboratory variables, presence of hypertension, dyslipidemia, alcohol consumption, and smoking were investigated. The grade of steatosis was estimated with fatty liver index (FLI), hepatic steatosis index (HSI), and controlled attenuation parameter (CAP by FibroScan®). The grade of fibrosis was estimated with fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), and liver stiffness (LS by FibroScan®).

Results: The mean age (61±9 vs. 55±12 years, $p<0.001$) was older, BW (75±17 vs. 71±14 kg, $p=0.04$), BMI (27±5 vs. 26±4 kg/m^2, $p=0.023$), and WC (93±12 vs. 89±10 cm, $p=0.008$) were higher in patients with CHD than in those without CHD. The CAP value (275±52 vs. 276±49 dB/m), FLI (51±30 vs. 46±28), HSI (40±7 vs. 38±6) and LS value (7.4±3.7 vs. 6.8±3.6 kPa) were not different between the two groups. However, FIB-4 (1.4±0.8 vs. 1.2±0.7, $p=0.018$) and NFS (-0.8±1.2 vs. -1.4±1.3, $p<0.001$) were higher in patients with CHD than those without CHD. Multivariate logistic regression analysis revealed that age [odds ratio (OR): 1.075, 95% confidence interval (CI): 1.039-1.113, $p<0.001$], hypertension (OR: 3.213, 95% CI: 1.575-6.556, $p=0.001$), and BW (OR: 1.040, 95% CI: 1.016-1.064, $p=0.001$) were significant risk factors for CVD.

Conclusions: The degree of steatosis and fibrosis was not associated with the risk of CHD in patients with DM. The risk factors of metabolic syndrome are more important for the development of CHD.

Keywords: Non-alcoholic fatty liver disease, Coronary heart disease, Diabetes mellitus, Controlled attenuation parameter, Liver stiffness

PE-206

Impact of Myosteatosis on Fibrosis Progression in Patients with Biopsy-Proven Non-Alcoholic Fatty Liver Disease: A Single Center, Prospective Study

Kyewhon Kim[1], Min-Kyu Kang[2], Jung Gil Park[2]

[1]Department of Internal Medicine, Yeungnam University Medical Center, Daegu, South Korea, [2]Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, South Korea

Aims: Burnt-out nonalcoholic steatohepatitis is defined as a reduction in hepatic fat accumulation in accordance with fibrosis progres-

sion in patients with non-alcoholic fatty liver disease (NAFLD). Although the association between NAFLD and sarcopenia was found, muscle alterations following the fibrosis progression in patients with NAFLD is not fully elucidated. We aimed to evaluate myosteatosis on progression of liver fibrosis in patients with biopsy-proven NAFLD.

Methods: This single-center prospective cohort study included 67 patients with biopsy-proven NAFLD who underwent abdominal computed tomography (CT). Based on a cross-sectional CT image at the specific level of 3rd lumbar vertebra, reduced muscle density was evaluated using the Hounsfield unit to assess myosteatosis. We analyzed the correlation between histopathological findings of liver fibrosis and reduced muscle density.

Results: Of 62 patients of biopsy-proven NAFLD, median age was 61 years (interquartile range: 37.0-69.0), 25 (40.3%) were male, and mean body mass index was 29.1 kg/m^2. Based on fibrosis stage, 30 patients were normal to significant fibrosis (F0-2), 16 were advanced fibrosis (F3), and 16 were cirrhosis (F4). Muscle density decreased significantly from F0-2 to F3 (p=0.007), while muscle density increased from F3 to F4, which was not statistically significant. (p=0.127) In the multivariate analysis, reduced muscle density (age & sex-adjusted odds ratio, 0.87; 95% confidence interval; 0.77-0.95, p=0.008) was associated with advanced fibrosis in patients with biopsy-proven NAFLD excluding cirrhotic patients.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age	1.05	(1.01, 1.10)	0.01			
Sex	3.92	(1.09, 16.72)	0.04			
Muscle HU	0.87	(0.77, 0.95)	0.008	0.87	(0.77, 0.95)	0.008

Conclusions: Myosteatosis is associated with fibrosis progression in patients with biopsy-proven NAFLD, excluding cirrhosis.

Keywords: NAFLD, Myosteatosis

PE-207

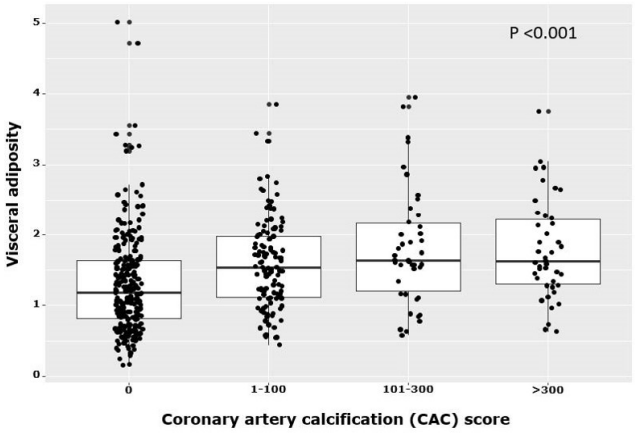
Impact of Visceral Adiposity for Coronary Artery Calcification Progression in Patients with Metabolic Dysfunction-Associated Fatty Liver Disease: Multicenter Cohort Study

Min Kyu Kang[1], KyeWhon Kim[2], Jung Eun Song[3], Jung Gil Park[1]

[1]College of Medicine, Yeungnam University, Internal Medicine, South Korea, [2]Yeungnam University Hospital, South Korea, [3]School of Medicine, Daegu Catholic University, South Korea

Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) as well as non-alcoholic fatty liver disease (NAFLD) is associated with coronary artery calcification (CAC) progression. Although body composition parameters are emerging as novel prognostic factors for NAFLD, the clinical significance of those on CAC progression in patients with MAFLD is lacking. We investigated the impact of body composition parameters on the CAC progression in patients with MAFLD.

Methods: A cross-sectional analysis of retrospective cohort study was conducted at two health promotion centers, including 457 MAFLD patients who performed ultrasound and abdominal & cardiac CT. Fatty liver was defined using ultrasound and presence of CAC as a CAC score > 0 was defined using cardiac CT. The CAC progression was classified by Greenland methods (0, 1 to 100, 101 to 300, and >300) Using cross-sectional CT images of 3rd lumbar vertebra, sarcopenia, visceral adiposity, and myosteatosis were defined.



Results: Median age was 57 years (interquartile range: 52.0-63.0) and 364 (79.6 %) were male. The presence of CAC was 44.6% and the CAC progression groups were identified by 253 (26.3%) in 1 to 100 group, 42 (9.2%) in 101 to 300 group, and 42 (9.2%) in >300 group, respectively. The visceral adiposity progression was correlated with the CAC progression (p<0.001). In the multivariate analysis, visceral adiposity (odds ratio, 1.79; 95% confidence interval; 1.14-2.83, p=0.011) was significant risk factors for presence of CAC, independent of pre-existing prognostic factors.

Conclusions: Visceral adiposity is associated with an CAC progression in patients with MAFLD, independent of traditional risk factors.

Keywords: NAFLD, Cardiovascular risk, Coronary calcification, Visceral adiposity

PE-208

MiR-4449-Merlin-TAZ Axis Regulates Fibrosis Progression in Non-Alcoholic Steatohepatitis

Young-Sun Lee, Yoonseok Lee, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon, Kwan Soo Byun

Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea

Aims: Although most non-alcoholic fatty liver disease (NAFLD) patients show benign clinical courses, non-alcoholic steatohepatitis (NASH) patients with hepatic fibrosis have poor prognoses compared to patients with non-alcoholic fatty liver (NAFL) or NASH without hepatic fibrosis. In this study, we aimed to analyze the role of miR-4449 in the progression of NASH-fibrosis.

Methods: Liver tissue and sera were collected from NAFLD patients who received liver biopsies in Korea University Guro hospital. MicroRNA sequencing, using sera, and mRNA sequencing, using liver tissue, were performed in patients with biopsy-confirmed NAFLD. To induce *in vitro* lipotoxicity in mice hepatocytes, HepG2 and Huh7 cells were treated with palmitic acids (PA). We transfected miR-4449 mimic or inhibitor into hepatocytes to explore the effect of miR-4449 during lipotoxicity. Mice were fed either a normal diet, a high fat

diet, or high fat with fructose for 24 weeks. The high fat with fructose group were also treated with miR-4449 mimic or miR-4449 inhibitor administered through tail veins.

Results: In total, 24 NAFLD patients were recruited, 15 patients had NAFL or NASH without fibrosis, whereas nine patients had NASH with fibrosis. In miRNA sequencing analysis, 31 miRNA sequences showed significant differences in expression levels between the two groups, with the expression of miR-4449 most prominently seen among miRNAs that showed higher expression levels in NASH-fibrosis compared to the NAFL or NASH without fibrosis group. PA treatment increased the expression level of miR-4449 in both supernatant and hepatocytes. On the other hand, the expression of merlin, which could be the target of miR-4449, decreased in PA-treated hepatocytes compared with vehicle-treated hepatocytes. In addition, merlin expression levels significantly decreased in NASH patients with fibrosis compared to NAFL and NASH patients without fibrosis. Hepatocytes with miR-4449 transfection mimic decreased merlin expression but exhibit increased phosphorylated TAZ expression, whereas hepatocytes transfected with miR-4449 inhibitor demonstrate increased merlin expression but decreased phosphorylated TAZ expression. The high fat with fructose group increased expression levels of miR-4449 in the liver compared with the high fat group. Treatment with miR-4449 inhibitors ameliorated liver steatosis and fibrosis, whereas treatment with miR-4449 mimics aggravated liver steatosis and fibrosis.

Conclusions: Patients with NASH-fibrosis showed increased miR-4449 expression. miR-4449 regulates merlin expression and TAZ phosphorylation in hepatocytes during lipotoxicity. miR-4449 may be of benefit as a novel therapeutic target in NASH-fibrosis.

Keywords: NASH, Micro RNA, Fibrosis

PE-209

Preventive Effect of Empagliflozin and Ezetimibe on Hepatic Steatosis in Adults and Murine Models

Dong Yun Kim[1,2,3], Kyu Sik Chung[4], Heon Yung Gee[3,5], Jun Yong Park[1,2]

[1]Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea, [3]Department of Pharmacology, Yonsei University College of Medicine, Seoul, Republic of Korea, [4]Department of Medicine, Yonsei University Graduate School of Medicine, Seoul, Republic of Korea, [5]Graduate School of Medical Science, Brain Korea 21 Project, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Even though many oral glucose-lowering or lipid-lowering agents have already been reported to improve hepatic steatosis to some degree, which drug had a more beneficial effect on hepatic steatosis among those drugs has not been precisely explored. We analysed the effect of empagliflozi, a selective sodium-glucose cotransporter 2 inhibitor, and ezetimibe on developing hepatic steatosis.

Methods: Using 4005,779 patients with type 2 diabetes mellitus (T2DM) or dyslipidemia provided by the Korean National Health Insurance Service (NHIS) between January 2015 and December 2015, we analyzed the odds ratio (OR) of fatty liver development (fatty liver index [FLI] >60). Additionally, we examined the metabolic effects of ezetimibe and empagliflozin in mice fed with a choline-deficient high-fat diet, mimicking the features of human NAFLD. The experiment for agents was performed for the non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) mouse models independently.

Results: In the NHIS data, ORs for the development of fatty liver were significantly lower in all treatment groups than in the reference group, which did not receive ezetimibe or empagliflozin. (Ezetimibe therapy; OR=0.962, empagliflozin therapy; OR=0.527, ezetimibe plus empagliflozin; OR=0.509 compared to reference therapy). Unlike non-alcoholic steatohepatitis mouse model, ezetimibe, empagliflozin, and combination therapy also reduced liver steatosis in the non-alcoholic fatty liver mouse model.

Conclusions: Compared with other agents, empagliflozin and/or ezetimibe treatment reduced the risk of developing hepatic steatosis. Our data suggest that empagliflozin or ezetimibe can be primarily considered in type 2 DM or dyslipidemia patients to prevent hepatic steatosis.

Keywords: Empagliflozin, Ezetimibe, NAFLD, Prevention

PE-210

L. Plantarum Ameliorates NASH-Related Inflammation via Upregulating L-Arginine Production

Dong Yun Kim[1,2], Heon Yung Gee[3], Jun Yong Park[1,2]

[1]Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea, [3]Department of Pharmacology, Yonsei University College of Medicine, Seoul, Republic of Korea

Aims: Lactobacillus is a potential probiotic and has therapeutic potential for several diseases, including the liver. However, it is unknown whether dietary supplementation with *L. plantarum* positively: affects non-alcoholic steatohepatitis (NASH). Therefore, we investigated the therapeutic potential of *L. plantarum* supplementation for treating NASH in a mouse model and to understand the mechanism by which it produced this effect if any.

Methods: We investigated the effect of *L. plantarum* on NASH by conducting transcriptomic analysis, metagenomic analysis, and immunohistochemistry analyses. We used a choline-deficient high-fat diet (CD-HFD) induced murine model that recapitulated the key features of human metabolic syndrome. Validation experiments were followed by the methionine-choline deficient (MCD) diet mouse model and liver organoid.

Results: *L. plantarum* treatment significantly improved several metabolic-phenotypes, such as insulin tolerance, and hepatic lipid content compared to the vehicle-group. RNA-sequencing analysis revealed that-inflammation-related pathways were significantly downregulated in the *L. plantarum* group. Shotgun metagenomic analysis showed that the genes of microbiota in the *L. plantarum* group were functioning in such a way that indicated that L-arginine biosynthesis had occurred. These results lead us to set L-arginine as a mediator of the gul-liver axis. This notion was supported by the elevated serum-arginine levels in the *L. plantarum* group. Using liver-organoids and mice fed on an MCD-diet, we show that L-arginine alone is sufficient to alleviate liver inflammation.

Conclusions: Our data demonstrated that the administration of *L.*

plantarum can improve NASH-associated phenotypes by increasing arginine production in the intestine.

Keywords: NAFLD, Probiotic, Lactobacillus, Gut liver axis

PE-211

ALT/AST Ratio: The Useful Predictive Marker for Insulin Resistance

Dong Kyun Koh[1], Seul Ki Han[1,3], Taesic Lee[2,3,4], Moon Young Kim[1,3*]

[1]Department of Internal Medicine, Younsei University Wonju College of Medicine, Wonju 26411, Korea, [2]Department of Family Medicine, Yonsei Univercity Wonju College of Medicine, Wonju 26411, Korea, [3]Regenerative Medicine Research Center, Yonsei University Wonju College of Medicine, Wonju 26411, Korea, [4]Division of Data Mining and Computational Biology, Institute of Global Health Care and Development, Wonju 26411, Korea

Aims: Insulin resistance (IR) is common pathophysiology in type 2 diabetes mellitus, cardiovascular disease, and non-alcoholic fatty liver disease. As increased to the prevalence of these diseases, screening the risk for IR becomes important to prevent disease progression. To predict insulin resistance in the general population, regardless of comorbidity, we analyzed the health examination data using ALT/AST ratio for analysis.

Methods: Insulin resistance (IR) is common pathophysiology in type 2 diabetes mellitus, cardiovascular disease, and non-alcoholic fatty liver disease. As increased to the prevalence of these diseases, screening the risk for IR becomes important to prevent disease progression. To predict insulin resistance in the general population, regardless of comorbidity, we analyzed the health examination data using ALT/AST ratio for analysis.

Results: Based on PCC, serum ALT in Korean men and women was positively related to four IR indices, including Glc, insulin, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), and HOMA-β. These positive relationships remained after selecting subjects diagnosed with diabetes or dyslipidemia, alcohol consumption, or subjects having general obesity or abdominal obesity. ALT/AST ratio was also robustly correlated with the four IR indices. In the multivariate LiR, when comparing ALT levels, ALT/AST ratio in Korean men exhibited better predictive performance for Glc and HOMA-β, besides, that in Korean women provided improved outcomes for all IR indices. Based on the prediction for the binary form of IR status, the ALT/AST ratio in Korean men and women could well predict HOMA-β and HOMA-IR, compared to the sole ALT level, respectively.

Conclusions: In the analysis that includes a large community-based population, ALT/AST ratio is a useful predictive marker compared with HOMA-IR. A simple, precise marker that is represented to ALT/AST could be a practical method to screen insulin resistance in the general population regardless of DM, alcohol intake, and gender.

Keywords: NAFLD, Insulin resistance

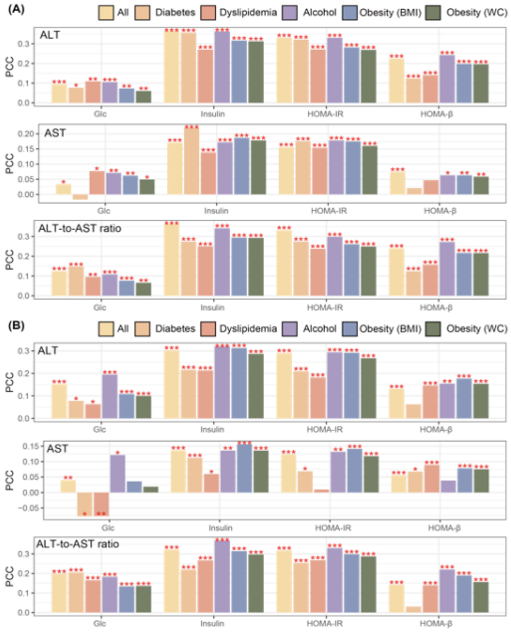


Figure 1. Association of liver profiles and IR indices. *, **, and *** denote *p*-value < 0.05, *p* < 0.01, and *p* < 0.001 that were calculated by Peason's correlation method, respectively. (Figure 1A : man, 1B: women) Based on PCC, serum ALT in Korean was positively related to four IR indices, including Glc, insulin, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), and HOMA-β. These positive relationships remained after selecting subjects diagnosed with diabetes or dyslipidemia, alcohol consumption, or subjects having general obesity or abdominal obesity. ALT/AST ratio was also robustly correlated with the four IR indices.

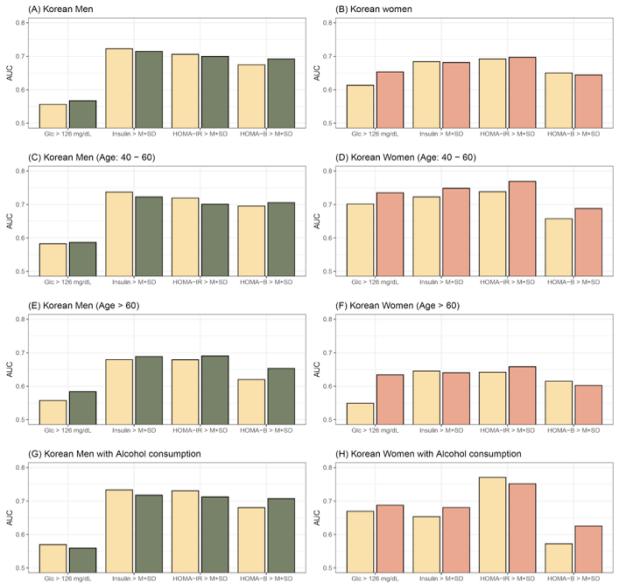


Figure 2. Classification performance of ALT and ALT-to-AST ratio for IR status. Abbreviations: Glc, fasting blood glucose; HOMA-IR, Homeostasis model assessment for insulin resistance; HOMA-β, HOMA for β cell.

The performance of ALT-to-AST ratio for classifying IR status was comparable to that of ALT. In Korean men, the best performance was resulted when classifying the IR status defined by serum insulin using serum ALT level. In case of Korean women, the best AUC value was provided when predicting the IR status based on HOMA-IR using ALT-to-AST ratio.

PE-212

The Effect of Thyroid Function on the Deterioration of NAFLD in a Prospective Cohort

Sae Kyung Joo, Won Kim

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul Metropolitan Government Boramae Medical Center, Seoul, South Korea

Aims: Thyroid hormones are strongly associated with increased intrahepatic steatosis and the degree of liver fibrosis. However, recent studies have shown inconsistent results in the relationship between thyroid status and nonalcoholic fatty liver disease (NAFLD). In this study, we aimed to evaluate the effect of thyroid function on liver fibrosis progression in a biopsy-proven prospective cohort.

Methods: A total of 632 subjects with biopsy-proven NAFLD (mean age, 52.35 years; 51.4% male) in Boramae Medical Center were enrolled in this study. We have divided the patients into three groups based on their thyroid-stimulating hormone (TSH) levels according to the Korea National Health and Nutrition Examination Survey (KNHANES) cutoff level (reference range 0.59 to 7.03 mIU/L). To determine changes in hepatic fibrosis, liver stiffness measured by FibroScan® was used.

Results: Of the subjects, 22 patients were elevated TSH and fibrosis progression was detected in 113 (17.9%) out of 632 patients. Subclinical hypothyroidism group (TSH >7.03 mIU/L) during follow-up evaluation is associated with progression of hepatic fibrosis. Multivariate analyses adjusted for age, sex, and body mass index (BMI) showed a significant independent association between the degree of thyroid dysfunction and liver fibrosis progression (for subclinical hypothyroidism: odds ratio, 2.25; 95% CI, 1.04-4.88 p=0.039).

Conclusions: TSH levels may be an important predictor of the development liver fibrosis in patients with NAFLD in this prospective cohort.

Keywords: Thyroid stimulating hormone, Nonalcoholic fatty liver disease, Liver fibrosis

PE-213

Magnetic Resonance Imaging-Proton Density Fat Fraction Correlates with Histologic Proven Hepatic Steatosis in Obese Patients: Single Center Study of Korea

Kwang Il Seo[1], Hyun joon Park[1], Sang Uk Lee[1], Byung Cheol Yun[1], Jung Wook Lee[1], Ki Hyun Kim[2], Yoonhong Kim[2], Kyung Won Seo[2]

[1]Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea, [2]Department of Surgery, Kosin University College of Medicine, Busan, Korea

Aims: Obesity is one of the important causes of Non-Alcoholic Fatty Liver Disease (NAFLD). Therefore, there are clinical needs for non-invasive diagnosis of NAFLD in obese patients. This study aimed to evaluation the efficacy and accuracy of MRI-proton density fat fraction (MRI-PDFF) and TE-controlled attenuation parameter (TE-CAP) in diagnosing hepatic steatosis of obese patient in Korea.

Methods: From 2021 to 2022, patients with a body mass index (BMI) of 30 kg/m^2 or higher who underwent bariatric surgery to reduce weight were reviewed retrospectively. The patients who had the all results of liver histologic assessment, MRI-PDFF and TE-CAP were analyzed.

Results: The total of 66 patients was reviewed, with 27 (40.9%) males and 39 (59.1%) females. The mean age was 38.45 (±9.957) years and the mean BMI was 41.138 (±8.376) kg/m^2. Histological findings were analyzed: steatosis 1.44 (±0.963), lobular inflammation 1.73 (±0.755), ballooning 1.61 (±0.523), NAS score 4.77 (±1.537), and fibrosis with METAVIR grade 1.55 (±8.863). As a result of non-invasive examination, TE-CAP was 334.09 (±51.619) and MRI-PDFF was 19.67 (±12.272). The correlation between histologic steatosis and non-invasive test were significant in TE-CAP as r=0.544 (p<0.0001) and in MR-PDFF as r=0.793 (p<0.0001), respectively. In addition, a significant correlation was also found between noninvasive MRI-PDFF and TE-CAP (r=0.496, p<0.0001).

Conclusions: The non-invasive test of both TE-CAP and MRI-PDFF are clinically useful for the evaluation of histological steatosis in obese patients. MRI-PDFF is thought to be more accurate in predicting hepatic steatosis than TE-CAP in obese patients in Korea.

Keywords: MRI-PDFF, TE-CAP, NAFLD, Obesity

PE-214

Comparison of Efficacy between Liraglutide and Phentermine/Topiramate in Obese Patients with Non-Alcoholic Fatty Liver Disease

Sung Jun Park[1], Yeon jung Ha[2], Joo Ho Lee[2], Kwank Sik Lee[2], Young Eun Chon[2]

[1]Department of Internal Medicine, CHA Gumi Medical Center, CHA University, Gumi, Korea, [2]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea

Aims: Anti-obesity drugs are known to improve hepatic inflammation in patients with nonalcoholic fatty liver disease (NAFLD). We aimed to compare the effect of liraglutide and phentermine/topiramate in obese NAFLD patients.

Methods: We retrospectively enrolled 411 obese NAFLD patients (BMI>25 and detection of fatty liver on ultrasound) who were treated with liraglutide (n=108) or phentermine/topiramate (n=303) for more than 12 months. Changes in laboratory data, anthropometric parameters, degree of steatosis and fibrosis were compared between two groups. Steatosis was assessed using the hepatic steatosis index and controlled attenuation parameter (CAP). Fibrosis was assessed using fibrosis index based on four factors (FIB4), NAFLD fibrosis score (NFS), and liver stiffness.

Results: The baseline mean body weight (phentermine/topiramate vs. liraglutide, 82.3 vs. 81.2 kg) and body mass index (30.1 vs. 29.8 kg/m^2) were similar between two groups. Both group showed significant reduction in steatosis (phentermine/topiramate: CAP, 319→290 dB/m; HSI, 40.6→37.0; liraglutide: CAP, 306→286; HIS, 40.3→39.3, all p<0.001) and fibrosis (phentermine/topiramate: NFS, -2.5→-2.6; LS, 6.7→5.3kpa; liraglutide: NFS, -2.4→-2.6, LS, 6.0→5.3kpa, all p<0.05) after 12 months or treatment compared to baseline. Phentermine/topiramate group showed significantly greater effect in weight loss

and steatosis reduction than liraglutide group (Δweight, −7.5 vs. −4.5 kg, p=0.001; ΔCAP: −29 vs. −8 dB/m, p<0.001).

Conclusions: Liraglutide or phentermine/topiramate treatment significantly ameliorated liver steatosis and fibrosis, but the effect on fibrosis improvement was minimal.

Changes between baseline and 12 months	phentermine/topiramate (n=303)	liraglutide (n=108)	P-value
Weight (kg)	**-7.5 ± 5.9**	**-4.5 ± 8.8**	**0.001**
Body mass index (kg/m^2)	**-2.6 ± 2.5**	**-1.5 ± 3.3**	**0.001**
Body fat (%)	**-2.7 ± 7.7**	**-4.3 ± 6.1**	**0.048**
Aspartate aminotransferase (IU/L)	-5 ± 16	-8 ± 19	0.084
Alanine aminotransferase (IU/L)	-9 ± 24	-9 ± 20	0.852
Serum albumin (g/dL)	0.0 ± 0.3	0.0 ± 0.4	0.670
Platelet count (×10^9/L)	-3 ± 40	2 ± 39	0.256
Hepatic Steatosis Index	**-3.554 ± 4.302**	**-0.937 ± 4.482**	**<0.001**
FIB-4	**0.021 ± 0.673**	**-0.120 ± 0.314**	**0.036**
NAFLD fibrosis score	-0.021 ± 0.673	-0.196 ± 0.829	0.300
CAP (dB/m)	**-29 ± 20**	**-8 ± 17**	**<0.001**
LS (kPa)	**-1.5 ± 3.4**	**-0.5 ± 1.6**	**0.024**

Variables are expressed as mean ± (SD).

Variables	Univariate		Multivariate	
	P-value	OR (95% CI)	P-value	OR (95% CI)
Age, years	0.703			
Male gender	0.674			
Weight (kg)	0.541			
Body mass index (kg/m^2)	0.287			
ΔBMI	**0.025**	**0.829 (0.703-0.977)**	**0.193**	**0.874 (0.714-1.071)**
Body fat (%)	0.618			
Diabetes mellitus	0.881			
Aspartate aminotransferase (IU/L)	0.760			
Alanine aminotransferase (IU/L)	0.643			
Serum albumin (g/dL)	0.063			
Platelet count (×10^9/L)	0.613			
Hepatic Steatosis Index	0.736			
ΔHepatic Steatosis Index	**0.045**	**0.907 (0.824-0.998)**	**0.850**	**1.012 (0.892-1.148)**
FIB-4	0.393			
NAFLD fibrosis score	0.681			
CAP (dB/m)	0.245			
LS (kPa)	0.333			
Phentermine/topiramate *vs.* Liraglutide	**<0.001**	**4.261 (1.924-9.439)**	**0.002**	**3.817 (1.618-9.006)**

Keywords: NAFLD, Liraglutide, Steatosis, Fibrosis

PE-215

Extrahepatic Malignancies in Metabolic Dysfunction-Associated Fatty Liver Disease: A Nationwide Cohort Study

Moon Haeng Hur[1], Min Kyung Park[1], Hye-Sung Moon[2,*], Hyunjae Shin[1], Sung Won Chung[1], Sungho Won[2,3], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, [2]RexSoft Inc., Seoul 08826, Korea, [3]Department of Public Health Sciences, Graduate School of Public Health, Seoul National University, Seoul, South Korea

Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD) encompasses heterogeneous fatty liver diseases associated with metabolic disorders. We aimed to evaluate the association between MAFLD and extrahepatic malignancies based on MAFLD subtypes.

Methods: This nationwide cohort study included 9,298,497 patients who participated in a health-screening program of the National Health Insurance Service of Korea in 2009. Patients were further classified into four subgroups: non-MAFLD, diabetes mellitus (DM)-MAFLD, overweight/obese-MAFLD, and lean-MAFLD. The primary outcome was the development of any primary extrahepatic malignancy, while death, decompensated liver cirrhosis, and liver transplantation were considered competing events. The secondary outcomes included all-cause and extrahepatic malignancy-related mortality.

Results: In total, 2,500,080 patients were diagnosed with MAFLD. During a median follow-up of 10.3 years, 447,880 patients (6.0%) with extrahepatic malignancies were identified. The DM-MAFLD (adjusted subdistribution hazard ratio [aSHR]=1.13; 95% confidence interval [CI]=1.11–1.14; p<0.001) and the lean-MAFLD (aSHR=1.12; 95% CI=1.10–1.14; p<0.001) groups were associated with higher risks of extrahepatic malignancy than the non-MAFLD group. However, the overweight/obese-MAFLD group exhibited a similar risk of extrahepatic malignancy compared to the non-MAFLD group (aSHR=1.00; 95% CI=0.99–1.00; p=0.42). These findings were reproduced in several sensitivity analyses. The DM-MAFLD was an independent risk factor for all-cause mortality (adjusted hazard ratio [aHR]=1.41; 95% CI=1.40–1.43; p<0.001) and extrahepatic malignancy-related mortality (aHR=1.20; 95% CI=1.17–1.23; p<0.001).

Conclusions: The diabetic or lean subtype of MAFLD was associated with a higher risk of extrahepatic malignancy than non-MAFLD. Therefore, risk stratification and different surveillance strategies based on the MAFLD subtypes are warranted.

Keywords: MAFLD, Fatty liver, Non-liver cancer, Diabetes

PE-216

Changes in Liver Stiffness and Controlled Attenuation Parameters of Transient Elastography according to Weight Change in Non-Alcoholic Fatty Liver Disease

Seong Kyun Na

Department of Internal Medicine, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Aims: The Controlled attenuation parameter (CAP) and the liver stiffness (LS) of transient elastography (TE) are widely used to measure the degree of fatty liver and liver fibrosis. We investigated whether there were significant changes in CAP and LS according to the amount of weight loss in patients with nonalcoholic fatty liver disease (NAFLD).

Methods: The patients with NAFLD at Jeju National University Hospital who had TE tests more than once and who lost weight during follow-up were analyzed. CAP and LS were compared between the time of the first test and the time of the weight was most lost during the follow-up.

Results: A total of 306 patients were analyzed. The median age was 52.5 years (interquartile range (IQR): 23.0), the median body mass index (BMI) was 28.34 (IQR: 5.35), the median CAP was 307 dB/m (IQR: 63), and the median LS was 6.7 kPa (IQR: 3.6). Patients were divided into 5 groups according to the weight loss (WL) percentage, and all groups showed significant CAP change (-21.00 in the 0 to 3% WL group, -17.00 in the 3 to 5% WL group, -36.50 in the 5 to 7% WL group, -26.00 in the 7 to 10% WL group, -80.00 in the more than

10% WL group, all p-values <0.05). The median LS change by the group was -0.40 in the 0 to 3% WL group, -0.10 in the 3 to 5% WL group, -0.10 in the 5 to 7% WL group, -0.40 in the 7 to 10% WL group, –0.70 in the more than 10% WL group, and was significant only in the more than 10% WL group (p=0.004). In multivariable analysis, weight change percentage and baseline BMI were significantly associated with CAP change, and weight change percentage, baseline BMI, and weight loss duration were significantly associated with LS change.

Conclusions: In patients with NAFLD, there was a significant correlation between weight loss and CAP, and LS decreases significantly when weight loss is greater than 10%.

Changes of variables of patients

Variables	All (n=306)	WL < 3% (n=97)	3% ≤ WL < 5% (n=82)	5% ≤ WL < 7% (n=46)	7% ≤ WL < 10% (n=43)	WL ≥ 10% (n=38)
BMI (kg/m²)	28.34 (5.35) 26.86 (4.96) (<0.001)	27.98 (3.55) 27.40 (3.71) (<0.001)	28.26 (6.81) 27.10 (6.65) (<0.001)	28.40 (4.97) 26.62 (4.49) (<0.001)	29.00 (5.52) 26.50 (5.33) (<0.001)	28.76 (6.35) 25.34 (4.87) (<0.001)
Changes in weight (kg)	-3.35 (3.70)	-1.30 (1.30)	-3.00 (0.90)	-4.50 (1.60)	-6.40 (2.40)	-10.05 (5.00)
Transient elastography						
CAP	307.00 (63.00) 270.50 (74.00) -28.00 (65.00) (<0.001)	309.00 (58.00) 286.00 (82.00) -21.00 (64.00) (<0.001)	302.00 (66.00) 278.00 (65.00) -17.00 (70.00) (<0.001)	305.50 (61.00) 270.00 (90.00) -36.50 (67.00) (<0.001)	302.00 (72.00) 265.00 (56.00) -26.00 (60.00) (<0.001)	315.50 (80.00) 239.00 (55.00) -80.00 (81.00) (<0.001)
LS	6.70 (3.60) 6.40 (3.50) -0.10 (2.80) (0.309)	6.50 (3.60) 6.90 (3.70) -0.40 (3.40) (0.151)	6.80 (3.50) 6.35 (3.40) -0.10 (2.90) (0.366)	6.65 (4.90) 6.75 (4.80) -0.10 (3.40) (0.768)	7.20 (3.10) 6.10 (2.81) -0.40 (2.70) (0.164)	6.40 (5.20) 5.65 (2.40) -0.70 (3.00) (0.004)

- Values are presented as median (IQR) in order of baseline value, follow-up value, changes of values, and p-values in parentheses.
- WL, weight loss

Keywords: NAFLD, Controlled attenuation parameter, Liver stiffness, Weight loss

PE-217

Essential Adolescent Lifestyle: Coffee Drinking Habit Contributes to Liver Disease: Evidence from Asia

Vivi Usmayanti[1], Helena Kartika Utami[2], Poby Karmendra[3]

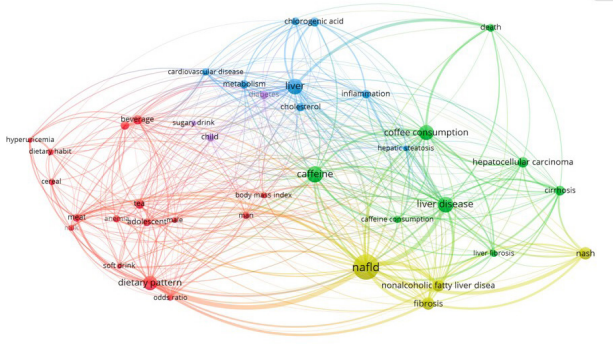
[1]Department of Management and Business, University of Dinamika Bangsa, Indonesia, [2]Medical Doctor, Bhayangkara Hospital, Jambi, Indonesia, [3]Department of Child Health, Faculty of Medicine, Andalas University, Dr. M. Jamil General, Hospital, Padang, Indonesia

Aims: This study aims to evaluate papers that discuss the trend of coffee consumption for adolescents contributing to preventing liver disease and Non-alcoholic fatty liver disease (NAFLD) and other liver diseases by discovering research that may be beneficial for coping and developing preventive ways with similar situations in the future.

Methods: This study used the review procedures with modifications, including co-word analysis, to map themes. The articles to be reviewed were identified by entering the search keywords "liver disease" AND "Coffee Consumption" and "liver" AND "young" in the Scopus database. After applying a set of criteria, 75 articles were used in the subsequent analysis in Asia countries.

Results: Results of this study showed the sophistication of drinking coffee in a young adult's lifestyle, having low liver disease, and its impact is seen in many countries in Asia. Several types of research found that coffee consumption decreases the risk of dying from liver disease, including liver-associated digestive disease, cirrhosis, and liver cancer. These five clusters identified by VOSviewer are related to coffee/caffeine consumption. As can be seen from the picture, in the green and yellow clusters, coffee/caffeine consumption is highly related to liver disease, NAFLD (non-alcoholic fatty liver disease), NASH, hepatocellular carcinoma, and cirrhosis. Then, the red clusters explain the association of the habit of adolescents to coffee/caffeine drinking habits. These networks indicate that many types of research supported the association between coffee/caffeine consumption with liver disease, especially in Asia, where coffee is a part of daily activity for studying, learning, and leisure, with the increasing of adolescent consumers. However, the mixing results showed different associations, with the most significant for coffee/caffeine drinker habit lowering the risk of liver disease.

Conclusions: This study found a significant coffee/caffeine consumption among young adults related to decreased risk of liver disease among young coffee drinkers.



Keywords: NAFLD, Coffee, Adolescent

PE-218

Severity of Fatty Liver Is Highly Correlated with the Risk of Hypertension and Diabetes: A Cross-Sectional and Longitudinal Cohort Study

Chin-I Shih[1,2], Kuan-Ta Wu[3], Meng-Hsuan Hsieh[3,5,6], Jeng-Fu Yang[3], Yi-Yu Chen[3], Wei-Lun Tsai[2,4], Wen-Chi Chen[2,4], Po-Cheng Liang[5], Yu-Ju Wei[5], Pei-Chien Tsai[5], Po-Yao Hsu[5], Ming-Yen Hsieh[5], Yi-Hung Lin[5], Tyng-Yuan Jang[5], Chih-Wen Wang[5,6], Ming-Lun Yeh[5,6], Chung-Feng Huang[5,6], Jee-Fu Huang[5,6], Chia-Yen Dai[5,6], Chi-Kung Ho[3], Wan-Long Chuang[5,6], Ming-Lung Yu[2,5,6]

[1]Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [2]School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver Disease, National Sun Yat-sen University, Kaohsiung, Taiwan, [3]Department of Preventive Medicine, and Health Management Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [4]Division of Gastroenterology, Department of Internal Medicine Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [5]Hepatobiliary Division, Department of Internal Medicine and Hepatitis Center, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [6]School of Medicine and Hepatitis Research Center, College of Medicine, and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan

Aims: Fatty liver disease (FLD) is associated with several metabolic derangements. We conducted a retrospective cross-sectional and longitudinal study to evaluate the role of FL severity in the risk of new-onset and co-existing hypertension (HTN) and diabetes mellitus (DM).

Methods: The cross-sectional cohort consisted of 41,888 adults who received health checkups in a tertiary hospital of Taiwan from 1999

to 2013. Of them, 34,865 without HTN and/or DM at baseline and within 1 year after enrollment were included as a longitudinal cohort (mean, 6.45 years for HTN; 6.75 years for DM). FL severity based on the degree or hepatic steatosis was assessed by ultrasound sonography.

Results: In cross-sectional cohort, 22,852 (54.6%) subjects had FL (18,203 [43.46%] mild FL and 4,649 [11.10%] moderate/severe FL); 13.5% (n=5,668) had HTN; and 3.4% (n=1,411) had DM. Moderate/severe FL and mild FL had significantly higher risks of existing HTN (adjusted odds ratio/95% confidence interval [CI]: 1.59/1.43–1.77 and 1.22/1.13–1.32, respectively). In longitudinal cohort, 3,209 and 822 subjects developed new-onset HTN and DM, respectively (annual incidence, 14.3 and 3.5 per 1,000 person-years; 10-year cumulative incidence, 14.35% and 3.89%, respectively). Moderate/severe and mild FL had significantly higher risks of new-onset HTN (adjusted hazard ratio [aHR]/CI: 1.54/1.34–1.77 and 1.26/1.16–1.37, respectively) and DM (aHR/CI: 5.88/4.44–7.81 and 3.22/2.56–4.07, respectively). Resolved FL during follow-up decreased the risk of HTN and/or DM.

Conclusions: Patients with FL are at high risk of prevalent and incident HTN and/or DM. The risk increases with the severity of FL.

Keywords: Hypertension, Diabetes, NAFLD, MAFLD, Incidence, Risk factor, Ultrasound sonography

PE-219

Diagnostic Performance of an Enhanced Liver Fibrosis Panel on the Identification of Fibrosis in Patients with High-Risk Non-Alcoholic Fatty Liver Disease

Yeo Wool Kang, Yang Hyun Baek, Sang-Yi Moon

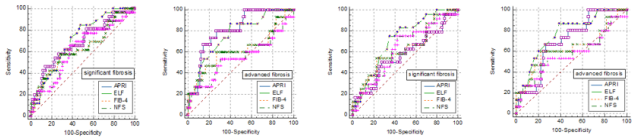
Department of Internal Medicine, Dong-A University College of Medicine, 32 Daeshingongwonro, Seo-gu, Busan

Aims: Non-invasive liver fibrosis tests have been developed to aid in the detection of fibrosis in patients with non-alcoholic fatty liver disease (NAFLD). This study aimed to assess the usefulness of the Enhanced Liver Fibrosis (ELF) panel as a screening tool specifically for individuals with non-alcoholic steatohepatitis (NASH) and fibrosis stage 2 or higher. The clinical efficacy of ELF was evaluated in comparison to other non-invasive tests within a clinical setting.

Methods: This single-center study enrolled 112 high-risk patients with ultrasonographic evidence of fatty liver, insulin resistance, diabetes, hypertension, and a body mass index (BMI) of 23 or higher. Serum tests, including the ELF panel, were conducted, and liver biopsies were performed on the following day. Non-invasive tests for liver fibrosis assessment, namely the aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 index (FIB-4), and NAFLD fibrosis score (NFS), and ELF, were employed, and the degree of fibrosis was determined based on the liver biopsy results. Subgroups were categorized according to the NAFLD activity score (NAS) and subjected to further analysis. The diagnostic performance of each non-invasive test was evaluated using the area under the receiver operating characteristic curve (AUROC).

Results: This study included 112 patients with NAFLD, with a mean (SD) age of 46.1 (13.6) years, and 66 (58.9%) were male. All patients underwent liver biopsies, revealing that 11 (9.8%) individuals had portal area fibrosis expansion (fibrosis stage 2), and 15 (13.4%) had bridging fibrosis (fibrosis stage 3), with no cirrhosis patients. Additionally, 63 patients (56.3%) had NAS 5 or higher. The assessment of significant fibrosis (stages F2-F4) in high-risk NAFLD patients showed AUROC values of 0.682, 0.633, 0.620, and 0.705 for APRI, FIB-4, NFS, and ELF, respectively. For diagnosing advanced fibrosis (stages F3-F4), the AUROC values were 0.807, 0.623, 0.545, and 0.764, respectively. In the subgroup analysis based on NAS, the AUROC values for APRI, FIB-4, NFS, and ELF were 0.573, 0.633, 0.628, and 0.717, respectively, for evaluating significant fibrosis among patients with a NAS score of 5 or higher. Notably, ELF demonstrated the highest AUROC value of 0.768 for the assessment of advanced fibrosis in patients with a NAS score of 5 or higher.

Conclusions: This study evaluated the clinical efficacy of the ELF panel as a screening tool for high-risk NAFLD patients with NASH and fibrosis stage 2 or higher. The results showed that ELF had superior diagnostic performance compared to other non-invasive tests, although the diagnostic performance was moderate. These findings suggest that non-invasive tests for identifying and managing high-risk NAFLD patients may not have high diagnostic value but can help exclude advanced fibrosis. The study contributes to enhancing the understanding of NAFLD patient management pathways and highlights the potential utility of ELF in clinical practice.



	High-Risk Patients		NAS ≥ 5 Patients	
	Significant fibrosis AUROC (95% CI)	Advanced fibrosis AUROC (95% CI)	Significant fibrosis AUROC (95% CI)	Advanced fibrosis AUROC (95% CI)
ELF	0.705 (0.611-0.787)	0.764 (0.674-0.839)	0.717 (0.590-0.822)	0.768 (0.646-0.864)
APRI	0.682 (0.587-0.767)	0.807 (0.722-0.876)	0.573 (0.443-0.696)	0.701 (0.573-0.809)
FIB-4	0.633 (0.537-0.722)	0.623 (0.526-0.713)	0.633 (0.504-0.750)	0.631 (0.501-0.749)
NFS	0.620 (0.524-0.710)	0.545 (0.449-0.640)	0.628 (0.498-0.745)	0.569 (0.439-0.692)

Fig 1. AUROC value for diagnosis of fibrosis in non-invasive tests
(A) High-Risk patients with Nonalcoholic fatty liver disease (B) NAS score of 5 or more patients in Nonalcoholic fatty liver disease

Keywords: Non-alcoholic fatty liver disease, Hepatic fibrosis, Enhanced liver fibrosis, Non-invasive test

PE-220

Risk Factors for Significant Fibrosis in Non-Alcoholic Fatty Liver Disease with a Low FIB-4 Level

Won Sohn, Yong Kyun Cho, Byung Ik Kim

Division of Gastroenterology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

Aims: Although FIB-4 index is widely used as a noninvasive biomarker to assess liver fibrosis in patients with nonalcoholic fatty liver disease (NAFLD), the diagnostic accuracy of FIB-4 index on significant fibrosis is not very high. This study aimed to investigate the risk factors for significant fibrosis in NAFLD patients who has a low FIB-4 level.

Methods: A cross-sectional study was conducted based on a cohort from a health examination program which included FIB-4 index and

magnetic resonance elastography (MRE). A low FIB-4 level was defined as FIB-4 <1.3. Significant fibrosis was defined as liver stiffness measurement (LSM) ≥2.97 kPa on MRE. We analyzed the risk factors for significant fibrosis (LSM ≥2.97 kPa) in NAFLD with FIB-4 <1.3.

Results: A total of 641 patients with NAFLD were included. The number of patients with FIB-4 ≥1.3 and FIB-4<1.3 was 138 (22%) and 503 (78%). Of 503 patients with FIB-4<1.3, the proportion of LSM ≥2.97 kPa on MRE is 5%. The univariable analysis showed that significant fibrosis (LSM ≥2.97) was associated with AST ≥40 U/L (odds ratio [OR]: 2.90, 95% confidence interval [CI]: 1.03–8.15, p=0.044), r-glutamyl transpeptidase (GGT) ≥60 U/L (OR: 2.60, 95% CI: 1.15–5.89, p=0.022), hypertension (OR: 2.54, 95% CI: 1.12–5.75, p=0.026), visceral obesity (increased waist circumference) (OR: 2.68, 95% CI: 1.10–6.54, p=0.030), and diabetes mellitus (OR: 4.64, 95% CI: 2.00–10.81, p<0.001). The multivariable analysis indicated that the risk factors for significant fibrosis in NAFLD with a low FIB-4 level were visceral obesity (OR: 2.48, 95% CI: 1.00–6.10, p=0.049), and diabetes mellitus (OR: 4.35, 95% CI: 1.86–10.21, p=0.001).

Conclusions: Significant fibrosis is present in NAFLD with a low FIB-4 level. An additional test is needed to assess liver fibrosis in NAFLD patients with diabetes mellitus and visceral obesity even though they have a low FIB-4 level.

Keywords: Nonalcoholic fatty liver disease, Fibrosis, FIB-4

PE-221

Differentiation of Liver Fibrosis Risk in Non-Alcoholic Fatty Liver Disease Patients Using Serum Mac-2 Binding Protein Glycosylation Isomer

Minna Kim[1], Yeo Wool Kang[1], Sang Yi Moon[1], Yang Hyun Baek[1], Se Young Jang[2], Dae Won Jun[3,4], Ki Tae Yoon[5,6], Young Youn Cho[7], Hoon Gil Jo[8], Ae jeong Jo[9]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea, [2]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Korea, [3]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea, [4]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, Korea, [5]Department of Internal Medicine, College of Medicine, Pusan National University, Busan, Korea, [6]Liver Center, Pusan National University Yangsan Hospital, Yangsan, Korea, [7]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea, [8]Division of Gastroenterology, Department of Internal Medicine, Wonkwang University College of Medicine and Hospital, Iksan, Korea, [9]Department of Information Statistics, Andong National University, Andong, Korea

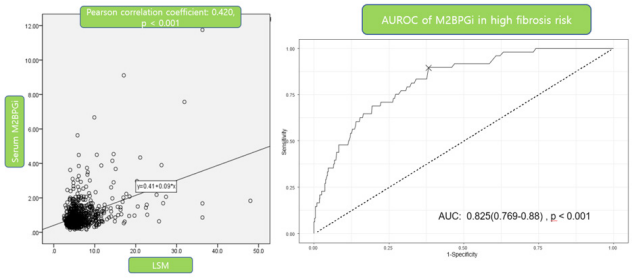
Aims: Non-alcoholic fatty liver disease (NAFLD) is an increasing cause of chronic liver disease worldwide. Although liver biopsy is the gold standard for evaluating liver fibrosis in NAFLD, it has several clinical limitations. Therefore, recently, diagnosis of liver fibrosis through a non-invasive method using an imaging modality has been widely spread, and among them, vibration-controlled transient elastography (VCTE) is the most widely used. After diagnosing the fibrosis risk in NAFLD patients by VCTE, we evaluated the performance of serum Mac-2 binding protein glycosylation isoform (M2BPGi).

Methods: From April 2015 to April 2022, we retrospectively reviewed 795 NAFLD patients who underwent VCTE and serum M2BPGi at Chung-Ang University Hospital (Seoul, South Korea), Hanyang University Hospital (Seoul, South Korea), Kyungpook National University Hospital (Daegu, South Korea), and Pusan National University Yangsan Hospital (Yangsan, South Korea). Liver stiffness measurement (LSM) was measured by VCTE in NAFLD patients, and patients below 8 kPa, 8 to 12 kPa, and above 12 kPa were classified into fibrosis risk of low risk, indeterminate risk and high risk, respectively. In addition, LSM is classified according to the criteria presented by Echosen (Paris, France), a manufacturer of VCTE, as follows; patients below 8.2 kPa, 8.2 to 9.6 kPa, 9.7 to 13.5 kPa, and more than 13.6 kPa were classified into fibrosis stages of F1, F2, F3, and F4, respectively. We analyzed the relationship between serum M2BPGi level and LSM with Pearson correlation, and the accuracy of serum M2BPGi in the diagnosis of fibrosis risk was calculated using area under the receiver–operator curve (AUROC) analysis. Statistical significance was considered at P-value <0.05.

Results: The average age of enrolled patients was 52.1 years. There were 387 (48.7%) males. Associated metabolic diseases were obesity (body mass index ≥ 25 kg/m^2) (n=437, 55.0%), diabetes (n=243, 30.6%), and dyslipidemia (n=357, 44.9%). The median levels of controlled attenuation parameter (CAP) was 278.0±56.8 dB/m. The grade of classifying fibrosis risk by VCTE is low risk in 650 (81.8%) patients, indeterminate risk in 97 (12.2%), and high risk in 48 (6.0%). According to several guidelines, the indeterminate risk and high risk additionally measure liver fibrosis with different test or proceed with liver biopsy, which is 18.2% in this study. The serum M2BPGi level was fair correlated with LSM (Pearson correlation coefficient: 0.420, p<0.001). The AUROCs of M2BPGi for indeterminate risk and high risk were 0.704 and 0.825, respectively. According to the liver fibrosis grade according to the criteria presented by Echosen, F0/1 is 657 (82.6%) patients, F2 is 45 (5.7%) patients, F3 is 52 (6.5%) patients, and F4 is 41 (5.2%) patients. The AUORC of M2BPGi in the group above F3 according to the criteria presented by Echosen is 0.710.

Conclusions: Serum M2BPGi showed a good diagnostic performance to the high fibrosis risk by LSM. Serum M2BPGi can be tested only by laboratory tests without additional diagnostic equipment such as VCTE, so it will be useful to simply differentiate the fibrosis risk of NAFLD patients during the primary medical institutions.

Keywords: Non-alcoholic fatty liver disease, Mac-2 binding protein glycosylation isomer, Vibration-controlled transient elastography



PE-222

NAFLD In Pediatrics

Eun Joo Lee[1*], Hye Won Lee[2*], Hong Koh[1†]

[1]Department of Pediatrics, Yonsei University College of Medicine, [2]Depart-

ment of Internal Medicine, Yonsei University College of Medicine

Aims: As childhood obesity is increasing worldwide, the prevalence of nonalcoholic fatty liver disease (NAFLD) in pediatrics and adolescents is also increasing. There are very few systematic studies and meta-analysis studies on the prevalence of pediatric NAFLD.

Methods: The MEDLINE, Korean Medical Database (KMBASE), Embase, Global Health, and Cochrane Library databases were searched from January, 1997, and October, 2020. Search term included: (1) NAFLD or steatosis (2) nonalcoholic or steatohepatitis (3) children, adolescents or teenager (4) prevalence, incidence or epidemiology. A random-effect meta-analysis model was used to estimate the prevalence of pediatric NAFLD.

Results: A total of 1,571 publications were found, of which 42 were included in the meta-analysis. Of these, 20 studies reported the prevalence in the general population and 26 studies reported that in the obese population. Worldwide pooled prevalence of pediatric NAFLD in general population was 13.5% (95% confidence interval [CI] 11.8-15.3) and in obese population was 46% (95% CI: 38-54). In addition, 13 studies in the general population and 11 studies in the obese population reporting the NAFLD prevalence by gender were also analyzed. The former was 10% (95% CI, 7-14%) for male and 8% (95% CI, 4-12%) for female, while the latter was 49% (95% CI: 38–61%) in males and 31% (95% CI: 2–44%) in females.

Conclusions: This study presented the increased global prevalence of pediatric NAFLD in the general and obese populations. As childhood obesity rapidly increase, epidemiological studies on the prevalence and incidence of NAFLD will be continuously needed.

Keywords: Pediatric, Nonalcoholic fatty liver disease, Meta-analysis

PE-223

Comparison of Transient Elastography and Shear Wave Elastography in Assessment of Liver Fibrosis in Egyptian Patients with NAFLD: A Single Center Experience

Mohamed Kohla[1], Ahmed El Fayoumi[1], Medhat Assem[1], Maha Elsabaawy[2], Rasha Abdelhafiz[2], Sally Waheed[3], Eman Abdelsameea[1]

[1]Hepatology and Gastroenterology department, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt, [2]Radiology department, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt, [3]Community department, National Liver Institute, Menoufia University, Shebin El-Kom, Egypt

Aims: Non-alcoholic fatty liver disease (NAFLD) has become the most common form of chronic liver disease worldwide. It is associated with significant complications such as cirrhosis, hepatocellular carcinoma (HCC) and overall mortality. Transient elastography (TE) and point shear wave elastography (pSWE) are noninvasive methods to diagnose fibrosis stage in patients with chronic liver disease. We aimed to compare the accuracy of the two methods to diagnose fibrosis stage in non-alcoholic fatty liver disease (NAFLD).

Methods: We enrolled 250 NAFLD patients who underwent clinical evaluation, laboratory characteristics, B-mode ultrasound and liver stiffness measurements (LSM) by pSWE, TE were evaluated on the same day.

Results: The mean age of studied patients was 41.5±10.7 years and male represented 56.0%. Kappa Agreement between (NAFLD TE and SWE) for F0 was (97.4%-89.4%) F1(80.3%-85.5%) F2(86%-91.5%) F3(80%-92.3%) F4(50%-100%) respectively with p-value <0.0001. The AUROC of TE for diagnosis of fibrosis stage F1, ≥ F2, ≥ F3, and F4 were 0.75, 0.87, 0.90, and 0.91, respectively. The corresponding AUROC of pSWE was 0.73, 0.82, 0.91, and 1.000, respectively. No statistically significant differences were found between TE and pSWE for diagnosis fibrosis stage ≥ F1, ≥ F2 ≥ F3, and F4.

Conclusions: Both Transient elastography (TE) and point shear wave elastography (pSWE) are the the same in the diagnosis fibrosis in NAFLD patients

Keywords: NAFLD, Transient Elastography, Shear wave elastography, Fibrosis

PE-224

Age-Specific Prevalence of Vitamin D Insufficiency in MAFLD Determined by Fatty Liver Index in Korean Adults

Kwang Min Kim, Bo Ram Sung, Deok Kil Lim, Kwang Cheol Koh

Department of Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Aims: The metabolic repercussions of vitamin D insufficiency, especially in association with Metabolic Dysfunction-associated Fatty Liver Disease (MAFLD), are gaining recognition. This study aims to investigate the relationship between serum vitamin D levels and MAFLD as characterized by the Fatty Liver Index (FLI) among Korean adults.

Methods: Data from 22,476 adults who attended health check-ups at Samsung Changwon Hospital, Korea, between January 2013 and July 2022 were meticulously analyzed. Participants were stratified based on serum vitamin D levels, and their FLI scores were utilized to determine the presence or absence of MAFLD.

Results: The prevalence of vitamin D insufficiency was notably higher in the MAFLD group (FLI ≥60) compared to the non-MAFLD group (FLI <30) (p=0.007). When segregated by gender and age.
For men, those within the MAFLD category persistently displayed increased rates of vitamin D insufficiency across all age brackets. The disparity was most evident in the 40-49 age group, with a prevalence of 62.5% in the MAFLD cohort versus 40.2% in the non-MAFLD cohort (p<0.001).
In women, a similar trend was observed. The MAFLD group showcased heightened rates of vitamin D insufficiency, especially in the 30-39 age group, where 65.1% of those with MAFLD were vitamin D insufficient, contrasting with 52.8% in the non-MAFLD group (p<0.001).
Across the board, individuals in the MAFLD category (FLI ≥60) consistently registered lower mean vitamin D concentrations compared to their non-MAFLD counterparts.

Conclusions: This investigation highlights a pronounced link between vitamin D inadequacy and the occurrence of MAFLD, as indicated by the FLI, in the Korean adult population.The findings illuminate the potential metabolic interplay of vitamin D in liver health, accentuating the need for more in-depth clinical investigations to fathom its broader implications.

Keywords: MAFLD, Health check-ups, Serum vitamin D levels, Fatty liver index

[Others]

PE-225

Liver Transplant

Javad Alizargar

Kashan University, Iran

Aims: Living doner liver transplantation (LDLT) has been acknowledged as a significant treatment for patients with an end-stage liver looking to beat the deficiency of organs and the holding up the mortality because of the waiting time. The aim of this study is to evaluate the knowledge, attitudes, and willingness for the organ donation in the population of Kashan.

Methods: The study population included 1026 participants from Kashan, Iran. The questionnaire consisted of 20 items designed to measure the participants' knowledge (10 item, 10 scores), attitudes (10 item, 10 scores), and willingness to LDLT (binary yes/no). The study assesses the relationship between knowledge and attitudes about LDLT and willingness to donate. A logistic regression model was used to find out which factor (knowledge or attitudes) is associated with whether or notsomeone is willing to donate. We adjusted for age, gender and education level.

Results: The response rate of the questionnaire was 63.3%. The mean public knowledge of the participants was 2.23 ±1.7, attitude score mean was 3.4 ±2.2. 76.3% of the participants were not willing to donate. Regression analysis showed that knowledge is an independent factor that changes the equation towards the willingness to donate with the odds ration of 1.6 (confidence interval 1.1-5.2) and attitude is also an independent and significant determinants of the willingness with the odds ration of 2.9 (confidence interval 1.8-6.9).

Conclusions: We conclude that regardless of age, sex, and educational status of the potential doners, both attitude and knowledge can be considered important factors that can have considerable effects on the willingness for donation. Healthcare system should aim the improvements in those aspects to overcome the waiting list mortality.

Keywords: Liver transplant, Donor, Attitude, Knowledge

PE-226

A Nationwide Study of Key Indicators for Eliminating Viral Hepatitis B and C in Korea

Chang Hun Lee[1], Gwang Hyeon Choi[2], Hwa Young Choi[3], Sojung Han[4], Young Eun Chon[5], Young Chang[6], Eun Sun Jang[2], Kyung-Ah Kim[7], Do Young Kim[8], Hyung Joon Yim[9], Hye-Lin Kim[10], Sook-Hyang Jeong[2], In Hee Kim[1]

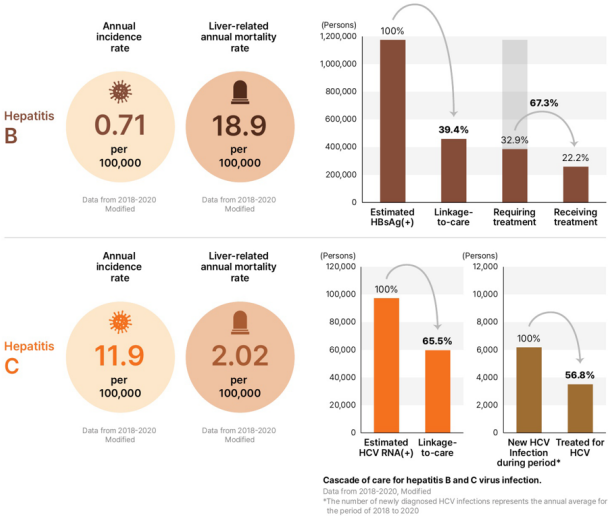
[1]Department of Internal Medicine, Jeonbuk National University Medical School, Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Korea, [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea, [3]Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, Korea, [4]Uijeongbu Eulji Medical Center, Department of Internal Medicine, Eulji University School of Medicine, Uijeongbu, Korea, [5]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea, [6]Department of Internal Medicine, Institute for Digestive Research, Digestive Disease Center, Soonchunhyang University College of Medicine, Seoul, Korea, [7]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea, [8]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; Yonsei Liver Center, Severance Hospital, Seoul, Korea, [9]Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Seoul, Korea, [10]College of Pharmacy, Sahmyook University, Seoul, Korea

Aims: To eliminate hepatitis B virus (HBV) and hepatitis C virus (HCV) according to the World Health Organization (WHO) criteria in 2021, this study investigated the national key indicators for eliminating viral hepatitis B and C in South Korea.

Methods: We analyzed the incidence, linkage-to-care, treatment, and mortality rates of HBV and HCV infection using the integrated nationwide big data of South Korea.

Results: According to data from 2018-2020, in South Korea, the incidence of acute HBV infection was 0.71 cases per 100,000 population; the linkage-to-care rate, defined as the number of patients who receive medical care out of the estimated HBV-infected patients, was only 39.4%. Among those who need hepatitis B treatment, the treatment rate was 67.3%, which was less than 80%, the WHO program index. The annual liver-related mortality due to HBV was 18.85 cases per 100,000 population, exceeding the WHO target of four, the most frequent cause of death was liver cancer (54.1%). The annual incidence of newly diagnosed HCV infection was 11.9 cases per 100,000 population, which is higher than the WHO impact target of five. Among HCV-infected patients, the linkage-to-care rate was 65.5%, while the treatment rate was 56.8%, below the targets of 90% and 80%, respectively. The liver-related annual mortality rate due to HCV infection was 2.02 cases per 100,000 population.

Conclusions: Many of the current indicators identified in the Korean population did not satisfy the criteria for validation of viral hepatitis elimination. A comprehensive national strategy should be developed urgently with continuous monitoring of the targets in South Korea.



Keywords: Viral hepatitis, Hepatitis B, Hepatitis C, Elimination

PE-227

Improving Hepatocellular Carcinoma Diagnosis from CT Scan Images with the Probabilistic Radial Basis Function Network Algorithm

Sahnaz Vivinda Putri[1], Rosmani Bahtiar[2], Elfiany Syafruddin[1]

[1]Health Management Laboratory, International University Semen Indonesia, [2]Department of Computer Science, International University Semen Indonesia

Aims: Hepatocellular carcinoma (HCC), the most prevalent form of liver cancer, poses significant challenges in diagnosis due to concealed symptoms and the limitations of current diagnostic methods. This study aims to address these limitations by developing an advanced and precise method for identifying HCC from CT scan images, employing the powerful Probabilistic Radial Basis Function (PRBF) network algorithm.

Methods: To classify HCC disease from CT scan images, we employed the state-of-the-art PRBF network algorithm. The images underwent meticulous preprocessing, including Gaussian filtering, segmentation through thresholding and morphology operators, and feature extraction using the robust gray-level co-occurrence matrix analysis. The dataset utilized in this study was sourced from The Cancer Imaging Archive (TCIA) and Radiopedia.org, ensuring a comprehensive and reliable foundation for our research.

Results: The PRBF network algorithm accurately identified Hepatocellular Carcinoma (HCC) from CT scan images with an impressive 95% accuracy. It showed excellent sensitivity (93%) and specificity (96%), ensuring reliable classification. The algorithm's efficiency enabled timely diagnoses and swift treatment interventions. The gray-level co-occurrence matrix method effectively recognized intricate HCC patterns. Advanced image preprocessing techniques enhanced accuracy by reducing noise and improving image clarity. These findings have significant implications for early HCC detection in individuals with chronic liver diseases.

Conclusions: This study convincingly demonstrates the remarkable potential of the PRBF network algorithm to significantly enhance the accuracy and efficiency of HCC diagnosis from CT scan images. By addressing the limitations of current diagnostic methods, our findings hold immense promise for improving clinical diagnosis and treatment of HCC in individuals affected by chronic liver diseases, such as hepatitis B or C. However, further research and development are imperative to optimize the performance of the classification system, thus paving the way for even greater advancements in this critical field.

Keywords: Hepatocellular Carcinoma, CT Scan, PRBF Network, Identification

PE-228

The Development of Viral Hepatitis in Asia: Systematic Review

Devi Yulia Rahmi

Department of Management, Universitas Andalas, Indonesia

Aims: Viral hepatitis is the seventh leading cause of mortality worldwide and is the only communicable disease where mortality is increasing (WHO, 2022). Viral hepatitis causes at least as many, if not more, deaths annually than TB, AIDS or malaria combined. There are five main hepatitis viruses: A, B, C, D and E. Most Asians acquire hepatitis B due to vertical transmission from their mothers during birth or later in life via child-to-child transmission (Asian Liver Disease, 2020). This study aims to see the development of viral hepatitis in Asia.

Methods: This research uses a systematic review method. We collected articles from 2010-2022 from an electronic database (pubmed.gov, springer, science direct, Gleneagles). The keywords used are Viral Hepatitis and Asia. Then as many as ten selected articles were reviewed to answer the purpose of this study.

Results: Asia has a very high burden of acute hepatitis; thus, a comprehensive study of the current burden and long-term trends of acute hepatitis in Asia is needed (Liu et al., 2022). Hepatitis B is common worldwide, especially in many parts of Asia and the Pacific Islands. Several countries in Asia are experiencing high development of Hepatitis B. In China, the reason for this increased HBV infection is unknown because hepatitis B has no clear transmission routes in many people in China. However, both neonatal infection and horizontal transmission during early childhood are still the most common routes (Wiki, 2023). In Asia, the burden of acute viral hepatitis was relatively high compared with the other four continents (Liu et al., 2022).

Conclusions: Viral hepatitis in Asia is increasing, for example, in China and in other Asian countries.

Keywords: Asia, Development, Sytematic review, Viral Hepatitis

PE-229

Study about Autoimmume Liver Disease in Asian Children: A Systematic Review

Ferza Alfath

Alumnus Department of Law Universitas Andalas, Indonesia

Aims: Autoimmune liver diseases occur when the body's immune system attacks the liver, causing inflammation. Little is known about the autoimmune liver disease (AILD) in Asian children. Several researchers have concluded several things about Autoimmune Liver Disease in Asian Children. So the purpose of this study is to see how far research on Autoimmune Liver Disease in Asian Children has progressed.

Methods: This research uses a systematic review method. We collected articles from 2013-2023 from an electronic database, lens.org. The keywords used are Autoimmune Liver Disease and Asian Children. Then as many as three selected articles were reviewed to answer the purpose of this study.

Results: A study by Lee et al. (2015) about clinical features and predictors of outcome in childhood AILD in an Asian population found that emission was achieved in the majority of patients with prednisolone and/or azathioprine therapy, delay in seeking diagnosis and treatment adversely affects the outcome of childhood AILD in Malaysia. Another research from Mieli-Vergani and Vergani (2015) said that in children and adolescents, AIH has a more aggressive course than in middle age and elderly patients and often presents acutely. The last one is from Mann et al. (2018), who discuss liver disease, the

initial investigations required and when referring to a specialist liver centre.

Conclusions: AILD in Asian Children research is starting to develop, for example, about clinical features and predictors of outcome in childhood AILD in an Asian, aggressive course, and liver disease

Keywords: Autoimmume liver disease, Asian children, Systematic review

PE-230

Live Donor Liver Transplantation (LDLT) in Asia: Systematic Review

Devi Yulia Rahmi

Department of Management, Universitas Andalas, Indonesia

Aims: Live Donor Liver Transplantation (LDLT) is an essential life-saving procedure for patients with acute liver failure and hepatocellular carcinoma. In adults, the most common reason for LDLT is liver cirrhosis, which refers to liver scarring. In children, biliary atresia is the most common reason for LDLT. The success of liver transplantation worldwide has brought increased demand for liver grafts. In Asia, the focus has been on living donor liver transplantation (LDLT), as this procedure is more acceptable in most Asian cultures. LDLT, initially devised for paediatric liver transplant patients, has evolved from using a left lobe graft to a right lobe graft for an adult recipient. This study aims to see the development of LDLT in Asia.

Methods: This research uses a systematic review method. We collected articles from 2010-2022 from an electronic database (pubmed.gov, springer, science direct, Gleneagles). The keywords used are LDLT and Asia. Then as many as three selected articles were reviewed to answer the purpose of this study.

Results: Asian liver transplant centres have been the world's pioneers, innovators, and technical advancement catalysts, especially concerning LDLT (Chen et al., 2013). Techniques to expand the living donor pool have also been adopted, like ABO-incompatible, paired exchange and dual lobe living donor liver transplants (Hibi et al. 2020). The unique combination of demographic, social, economic and political factors in Asia will ensure that LDLT remains the predominant form of liver transplantation. In one of the samples of LDLT in Hongkong patients, 74.9% met the UCSF criteria, and 64.5% met the Milan criteria. A 5-year overall and disease-free survival rate of 78.9% and 76.3% were achieved (Mok et al., 2022).

Conclusions: LDLT in Asia is starting to develop. The technique often used is ABO-incompatible, paired exchange and dual lobe living donor liver transplants.

Keywords: Live donor liver transplantation, Asia, Sistematic review

PE-231

Global Interest in Hepatitis B Viral Infection, Risk factors, Neurological Sequelae, and Neuroimaging Tools in Neonatal Jaundice Using Google Trends

Albert Dayor Piersson[1*], Klenam Dzefi-Tettey[2], Joseph Arkorful[3], Isaac Frimpong Brobbey[4], Philomena Asakeboba[5]

[1]University of Cape Coast, School of Allied and Health Sciences, Department of Imaging Technology and Sonography, Cape Coast, Central Region, [2]Korle-bu Teaching Hospital, Department of Radiology, Korle-bu, Accra, [3]University of Cape Coast, School of Allied and Health Sciences, Department of Imaging Technology and Sonography, Cape Coast, Central Region, [4]University of Cape Coast, School of Allied and Health Sciences, Department of Imaging Technology and Sonography, Cape Coast, Central Region, [5]University for Development Studies, School of Nursing and Midwifery, Department of Advanced Nursing Practice, Tamale, Northern Region, Ghana

Aims: In the current study, we analyzed global search interests related to hepatitis B viral infection, associated risk factors, neurological sequelae, and neuroimaging tools in the context of neonatal jaundice.

Methods: We evaluated Google Trends data from January 2010-December 2022 on global search interests in hepatitis B viral infection, related risk factors, neurological sequelae, and neuroimaging tools in neonatal jaundice.

Results: Search interest by region varied widely across continent. Search interest in neonatal jaundice was significantly associated with search interests in all hepatitis B-related terms, risk factors (i.e., exclusive breast feeding, ABO incompatibility, G6PD deficiency, sepsis, low gestational age, rhesus incompatibility, preterm birth, liver disease, cirrhosis, and hepatocellular carcinoma), brain, neurodevelopmental disorders, and their sequalae, and non-ionizing imaging modalities (i.e., ultrasound and MRI). Predictors of interest in neonatal jaundice were interests in HBsAg (β=.441, p=<.000), exclusive breast feeding (β=.120, p=.008), ABO incompatibility (β=.113, p=.034), sepsis (β=.174, p=<. 000), rhesus incompatibility (β=.074, p=.038), and preterm birth (β=.238, p=.000), brain (β=.411, p=<.000), kernicterus (β=.187, p=.001), seizures (β=.520, p=<.000), autism spectrum disorder (β=.286, p=<. 000), developmental delay (β=.161, p=.036), hearing loss (β=.378, p=.001), neurodevelopmental disorder (β=.275, p=<.000), MRI (β=.341, p=.001), and Doppler ultrasound (β=.383, p=<.000).

Conclusions: The findings highlight the diverse regional variations and significant associations demonstrated between the various search interests, demonstrating the complex interplay of factors that influence public knowledge and awareness in this domain. Further research may focus on targeted interventions for an improved maternal, foetal and neonatal healthcare education and outcomes.

Keywords: Hepatitis B viral infection, Neurodevelopmental disorders, Neurological sequelae, Neuroimaging

PE-232

The Clinical Course and Outcomes of Patients with COVID-19 Given Ursodeoxycholic Acid, Transmetil or Silymarin: A Retrospective Cross-Sectional Single Center Study

Godofredo Vistal[1,2], Rejine Divinagracia[1,2], Gentry Dee[1,2]

[1]Department of Medicine- St. Luke's Medical Center - Global City, [2]Institute of DIgestive and Liver Disease - St. Luke's Medical Center, St. Luke's Medical Center, Philippines

Aims: This study aimed to determine the clinical course and outcomes of patients who had transaminitis in COVID-19 infection and were started on the following medications, whether singly or in combination, ursodeoxycholic acid (UDCA), Silymarin and Transmetil.

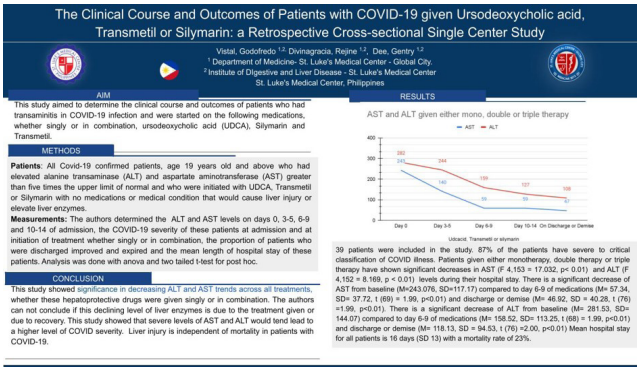
Methods: Patients: All Covid-19 confirmed patients, age 19 years old and above who had elevated alanine transaminase (ALT) and aspartate aminotransferase (AST) greater than five times the upper limit of normal and who were initiated with UDCA, Transmetil or Silymarin wheter in combination or in monotheraphy with no medications or medical condition that would cause liver injury or elevate liver enzymes.

Measurements: The authors determined the ALT and AST levels on days 0, 3-5, 6-9 and 10-14 of admission, the COVID-19 severity of these patients at admission and at initiation of treatment, the proportion of patients who were discharged improved and expired and the mean length of hospital stay of these patients. Analysis was done with Anova and two tailed t-test for post hoc.

Results: 39 patients were included in the study. 87% of the patients have severe to critical classification of COVID illness. Patients given either monotherapy, double therapy or triple therapy have shown significant decreases in AST (F 4,153=17.032, p<0.01) and ALT (F 4,152=8.169, p<0.01) levels during their hospital stay. There is a significant decrease of AST from baseline (M=243.076, SD=117.17) compared to day 6-9 of medications (M=57.34, SD=37.72, t (69)=1.99, p<0.01) and discharge or demise (M=46.92, SD=40.28, t (76)=1.99, p<0.01). There is a significant decrease of ALT from baseline (M=281.53, SD=144.07) compared to day 6-9 of medications (M=158.52, SD=113.25, t (68)=1.99, p<0.01) and discharge or demise (M=118.13, SD=94.53, t (76)=2.00, p<0.01) Mean hospital stay for all patients is 16 days (SD 13) with a mortality rate of 23%.

Conclusions: This study showed signficant decrease in ALT and AST trends across all treatments, whether these hepatoprotective drugs were given singly or in combination. The authors can not conclude if this declining level of liver enzymes is due to the treatment given or due to recovery. This study showed that severe levels of AST and ALT would tend lead to a higher level of COVID severity. Liver injury is independent of mortality in patients with COVID-19.

Keywords: COVID-19, Ursodeoxycholic acid, Transmetil, Silymarin, AST, ALT



PE-233

Analysis of Total Protein Concentration and Antioxidant Activity in Pesticide-Highly Contaminated Rice

Nisrin Abd Kadir

School of Fundamental Science, Universiti Malaysia Terengganu, Terengganu, Malaysia

Aims: The world's second-most important crop, rice, requires high production levels to meet demand. Nonetheless, farmers often used risky practices, such as the use of highly concentrated insecticides, to deal with pest issues. Various reviews have highlighted the adverse effects of pesticide-contaminated foods, which can elevate the risk of liver cancer, including hepatitis, in humans. In light of the fact that humans consume rice on a daily basis for an extended length of time (years to a decade), it is important to examine the impact of these pesticides on rice and how rice reacts to high pesticide concentrations.

Methods: Hence, to determine the impact of high pesticide concentrations on total protein and antioxidant activities, this study was selected. In this study, the Oryza sativa variety MR263 was selected, and it was planted using a 3:2:½:½ ratio of soil, sand, organic fertiliser, and peat moss. After that, rice was exposed to pesticide contamination four and six times higher than normal before being tested for total protein and antioxidant activity using the Bradford and APX tests, respectively, through a UV-Vis Spectrophotometer.

Results: According to our findings, when rice was polluted with pesticides, total protein and ascorbate peroxidase activity (an antioxidant) showed significant alterations (p<0.05). They can be observed in samples that were exposed to pesticides at a six-fold concentration.

Conclusions: As a result of the accumulation of heavy metals in rice plants, spraying pesticides at higher concentrations may cause oxidative stress, which could have harmful health impacts on rice consumers, including an increased risk of liver cancer and other liver diseases. Hence, in order to help with the development of biosensors for identifying foods contaminated with high quantities of pesticides, precise identification of antioxidant protein in rice plants is necessary.

Keywords: Ascorbate peroxidase, ANOVA-analysis of variance

PE-234

Randomized Controlled Trial: The Effect of Oral Methylprednisolone versus Placebo to Reducing Level Liver Enzyme in Cholestasis Infants

Anindya Kusuma Winahyu[1], Rendi Aji Prihaningtyas, Firyal Nadiah Rahmah, Bagus Setyoboedi[2], Sjamsul Arief

[1,2]Department of Child Health, Dr. Soetomo General Hospital, Surabaya, Indonesia

Aims: Cholestatic liver disease is a disease that causes liver damage and fibrosis owing to bile stasis. Methylprednisolone is anti-inflammatory agent. This study aims to analyzed effect of methylprednisolone therapy in decreasing level of Gamma Glutamyl Transferase (GGT), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) in infants with cholestasis.

Methods: A Double blinded-randomized control trial enrolled patients with cholestasis age between 2-12 weeks who met inclusion criteria: jaundice, acholic stool, and dark urine was performed in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (ISRCTN registry). Double blinded treatment was administered into methylprednisolone (2 mg/kg/day divided into 2 times a day) dan placebo group in 2 weeks. Level of GGT, AST, and ALT before and after

administered between groups were evaluated. Clinician-recorded adverse events, patient-reported symptoms, and medication nonadherence. Analysis was performed using SPSS with p significant <0,05.

Table 1. Basic characteristic

Variable	Methylprednisolone n (%) Mean ± SD	Placebo n (%) Mean ± SD	p
Age	8,39 ± 3,11	8,98 ± 2,80	0,54[a]
Duration of illness (week)	6,24 ± 3,343	6,09 ± 3,010	0,89[a]
	Median (Min – Max)	**Median (Min – Max)**	
Onset of jaundice (week)	1 (1-7)	2 (1-8)	0,27[b]
Onset of acholic stool	4 (4-6)	4 (1-8)	0,45[b]
Onset of dark urine	4 (1-4)	4 (1-4)	0,68[b]
	n (%)	**n (%)**	
Sex			
Male	17 (85,0)	8 (44,4)	0,02[c]
Female	3 (15,0)	10 (55,6)	
Hepatomegaly			
Yes	20 (100,0)	18 (100,0)	1,00[d]
No	0 (0,0)	0 (0,0)	
Splenomegaly			
Yes	2 (10,0)	3 (16,7)	0,65[d]
No	18 (90,0)	15 (83,3)	
Ascites			
Yes	0 (0,0)	3 (16,7)	0,09[d]
No	20 (100)	15 (83,3)	
Abdominal USG			
Normal	18 (90,0)	14 (77,8)	0,39[d]
Abnormal	2 (10,0)	4 (22,2)	
Liver biopsy			
Intrahepatic cholestasis	8 (57,1)	8 (66,7)	0,70[d]
Extrahepatic cholestasis	6 (42,9)	4 (33,3)	

SD: Standard Deviation; Min: Minimum; Max: Maximum
a: Independent Samples T Test; b: Mann-Whitney Test; c: Chi-Square Tests; d: Fisher's Exact Test; p significant < 0,05

Table 2. Laboratory measurement of the subjects

Variable	Methylprednisolone	Placebo	p
	Median (Min – Max)	**Median (Min – Max)**	
GGT (U/L)	170 (58,00-563,00)	144,50 (37,02 – 1481,1)	0,53[a]
AST (U/L)	187,05(15,00-911,00)	206,90 (29,90 – 759,50)	0,78[a]
	Mean ± SD	**Mean ± SD**	
ALT (U/L)	170,43 ± 134,43	205,46 ± 125,06	0,41[b]

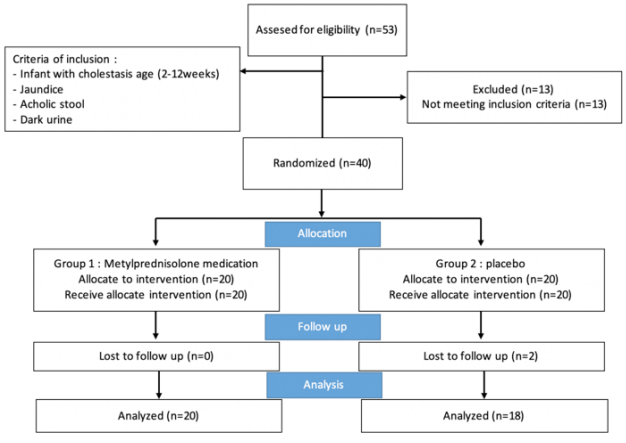
SD: Standard Deviation; Min: Minimum; Max: Maximum
[a]Mann-Whitney Test; [b]Independent Samples T Test; p significant< 0,05

Table 3. Effect of Methylprednisolone vs Placebo in GGT, AST, and ALT

	Methylprednisolone	Placebo	p
GGT (U/L)	208,50 (40,00 - 1119,00)	248,50 (62,00 - 1189,00)	**0,04[b]**
AST (U/L)	121,00 (39,10 - 330,00)	176,30 (50,00 - 604,29)	**0,01[a]**
ALT (U/L)	182,16 ± 140,21	203,20 ± 111,35	0,64[a]

[a]Paired Samples T Test; [b]Wilcoxon Signed Ranks Test;

Figure 1. CONSORT flow Diagram



Results: A total 40 infants (age=8,75±2,88 weeks) were double blinded randomize to administered methylprednisolone (n=20) vs placebo (n=18). There were no difference in both group before administered in the ratio of GGT level (170 (58,00 - 563,00) U/L vs 144,50 (37,02-1481,10) U/L, *p*=0,53)), AST level (187,05 (15,00 - 911,00) U/L vs 206,90 (29,90-759,50) U/L, *p*=0,78)), and ALT level 170,43±134,43 U/L vs 205,46±125,06, *p*=0,41). After 2 weeks of administered methylprednisolone, GGT level (208,50 (40,00 - 1119,00) U/L vs 248,50 (62,00 - 1189,00) U/L, *p*=0,04) and AST level 121,00 (39,10 - 330,00) U/L vs 176,30 (50,00 - 604,29) U/L, *p*=0,01) was significantly decreased compare to placebo.

Conclusions: In conclusion, two weeks after administered methylprednisolone showing greater decrease level GGT and AST in infants with cholestasis. Decreasing level GGT may associated with decreasing inflammatory in bile duct.

Keywords: Liver enzyme test, Cholestasis, Methylprednisolone, Infants

PE-235

Bile Acids Are Associated with Drug Induced Liver Injury (DILI) in Patients on Anti-Tuberculous Therapy (ATT)

Ashok Kumar[1], Nusrat Shafiq[1], Ajay K. Duseja[2], Ashutosh N. Aggarwal[3], Navneet Sharma[4], Nandita Kakkar[5], Samir Malhotra[1]

[1]Department of Pharmacology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [2]Department of Hepatology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [3]Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [4]Department of Internal Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, [5]Department of Histopathology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Aims: Total bile acids (TBA) and other liver enzymes have been biomarkers of liver injury for decades. To identify novel serum biomarkers with greater specificity for liver injury is current need. The objective of this study was to assess the individual bile acids (IBA) as a new biomarker in ATT-DILI patients.

Methods: In this study, TB patients were divided into two groups (Control and DILI). Control group include the adults who were exposed to ATT but did not develop DILI. DILI patients were included based on the following threshold criteria: (1) Exposure within 3 months of ATT, (2) Aspartate transaminase (AST) and/or Alanine transaminase (ALT) > 2 x upper limit of normal (ULN) or Rise in Alkaline phosphatase (ALP)> 2 x ULN or Rise in Bilirubin > 2 x ULN with any rise in AST and ALT elevation. LC-MS/MS method used to measure three IBA; deoxycholic acid (DCA), glycocholic acid (GCA), and taurocholic acid (TCA).

Results: 78 patients (36 in control and 42 in DILI group) recruited who were on ATT. LC-MS/MS method used to analyse the plasma samples for the IBA estimation. The baseline characteristics and LC-MS/MS data are given in Figure. The LFTs value were significantly higher in DILI group. 40.48% patients show cholestatic type injury followed by hepatocellular (38.09%) and mixed type (21.43%). Out of 42, 14 patients (33.33%) had jaundice while 2 patients (4.76%) died during the treatment. The mean concentration of the GCA and TCA

were 7644 ng/mL (p<0.0001) and 4607 ng/mL (p<0.0002) respectively for DILI patient. The DCA level (28.9 ng/mL) was significantly (p<0.02) lesser in the control group.

Table 1: Baseline Characteristics and individual bile acids (IBA) of the Participants

	Control	DILI
Participants (n=78)	36	42
Age (year) (Mean, SD)	33 (14.89)	36 (14.57)
Age group		
12-40 years	27 (75.00%)	28 (66.67%)
41-60 years	7 (19.44%)	11 (26.19%)
> 60 years	2 (5.56%)	3 (7.14%)
Sex		
Male	20 (55.6%)	20 (47.62%)
Female	16 (44.4%)	22 (52.38%)
Liver function tests (Mean, SD)		
Total Bilirubin (mg/dL)	0.45 (0.20)	9.4 (33.40)
AST (U/L)	32.7 (11.23)	225.0 (319.00)
ALT (U/L)	24.9 (14.34)	242.3 (344.08)
ALP (U/L)	103.2 (23.04)	261.4 (479.95)
Type of injury		
Hepatocellular	NA	16 (38.09%)
Cholestatic	NA	17 (40.48%)
Mixed	NA	9 (21.43%)
Severity		
Severe	NA	14 (33.33%)
Moderate	NA	3 (7.14%)
Mild	NA	25 (59.52%)
Jaundice	NA	14 (33.33%)
% survival	100	95.24
Individual bile acids (IBA) (Mean, SD) (n=36+36)		
DCA (p <0.02) (ng/mL)	58.3 (62.33)	28.9 (39.60)
GCA (p <0.0001) (ng/mL)	599.3 (490.83)	7644.6 (10067.55)
TCA (p <0.0002) (ng/mL)	97.0 (75.90)	4607.0 (6857.48)

Data are presented as n, mean (SD) on n (%), unless otherwise stated. NA- Not applicable.

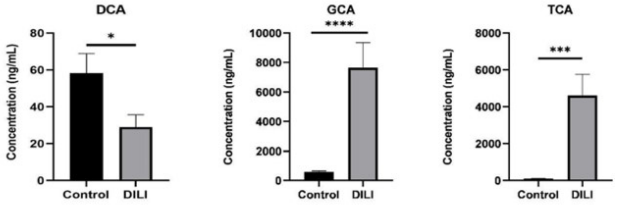


Figure 1: Plasma level of individual bile acids- DCA, GCA and TCA

Conclusions: Overall, our results indicate that DCA, GCA and TCA are promising biomarkers for ATT induced liver injury. It may be useful for diagnosis in DILI.

Keywords: Bile acids, Biomarkers, DILI, LC-MS/MS

PE-236

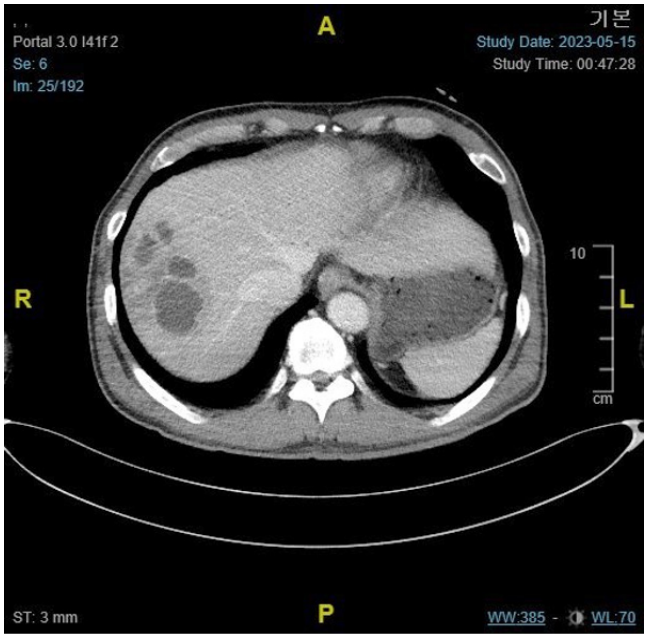
A Case of Concomitant Liver and Brain Abscesses Caused by Streptococcus Intermedius

Gum Mo Jung, Sang Gyeun Kim

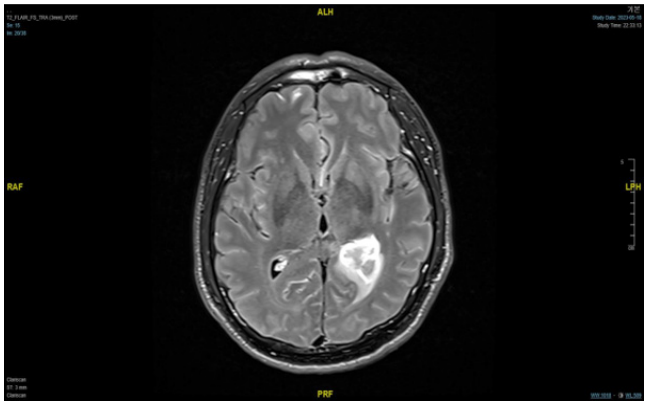
Department of Internal Medicine-GI/Hepatology, Jesus hospital, Jeonju, Republic of Korea

Aims: Concomitant liver and brain abscesses is rare infectious disease. *Streptococcus intermedius* is a beta-hemolytic, nonmotile, catalase-negative, gram-positive member of the Streptococcus anginosus group. Even this group is part of the normal human microbiota in the respiratory, gastrointestinal, and genitourinary tracts, they can cause purulent infections and abscesses in the heart, brain, liver, lungs, spleen, peritoneum, and appendix.

Methods: Especially, *S. intermedius* is the most pathogenic of the group, having significantly longer hospital stays and significantly higher mortality rates.



Results: CASE: We describe a case of a 59-year-old male, who presented with fever, headache and abdominal discomfort. He had a history of diabetes. Abdomen CT showed newly defined multiple irregular fluid density abscesses in right liver, and brain CT didn't reveal any acute lesions. Even though empirical antibiotics and liver abscess catheter drainage, he had a headache with fever. On hospital 5th day, brain MRI revealed 2.8cm brain abscess and *Streptococcus intermedius* was cultured in liver abscess fluid.



Conclusions: So, we report a case of concomitant liver and brain abscesses with rapid and aggressive behavior like complicated brain hemorrhage even using susceptible antibiotics.

Keywords: Liver abscess, Brain abscess

PE-237

High Serum IL-15 Level and Intrahepatic NKG2D Expression Are Associated with the Cholestatic Liver Injury in Patients with Drug-Induced Liver Injury

Ji Won Han[1,2+], Jong Geun Park[1+], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Pil Soo Sung[1,2*]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, 06591, Republic of Korea, [2]Division of Gastroenterology and Hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea

Aims: IL-15-mediated bystander CD8 T-cell activation and its association with liver damage has been reported in acute viral hepatitis, but its role in drug-induced liver injury (DILI) is unknown.

Methods: We collected serum and liver biopsy samples from 26 patients with DILI. Medical records were reviewed, and a pathologist performed histologic examinations using the hepatic activity index and immunohistochemistry (IHC) for CD3/CD68/CD38. Additionally, enzyme-linked immunosorbent assay (ELISA) for serum IL-15 levels and IHC for CD8/NKG2D were performed.

Results: The serum IL-15 level was significantly higher in DILI patients compared to healthy controls and was lower in patients who resolved within 30 days compared to the non-resolution group. The serum IL-15 level was correlated with total bilirubin (TB) and alkaline phosphatase levels but not with aspartate/alanine aminotransferases. In the histologic examinations, IL-15 levels were not correlated with lobular/porto-periportal activities or fibrosis and were not associated with CD3/CD68/CD38 positivity. When we divided the patients into IL-15 high (n=15) and low (n=11) groups, the IL-15hi group showed significantly higher intrahepatic CD8 and NKG2D levels. Intrahepatic NKG2D expression was positively correlated with the TB level and Model for End-Stage Liver Disease (MELD) score.

Conclusions: These findings suggest that IL-15-induced NKG2D-mediated liver injury might be associated with cholestatic liver injury in DILI. Further studies are needed to identify the intrahepatic immune-cell population associated with these observations.

Keywords: Drug induced liver injury, IL-15, NKG2D, CD8

PE-238

High Serum CXCL13 Level Is Associated with the Severe Cholestatic Liver Injury in Patients with Drug-Induced Liver Injury

Ji Won Han[1,2+], Jong Geun Park[1+], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Wonhee Hur[3], Pil Soo Sung[1,2*]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, [2]Division of Gastroenterology and Hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, [3]Division of Chronic Viral Disease Research, Center for Emerging Virus Research, Korean National Institute of Health

Aims: Several serum cytokines were reported to be elevated in drug-induced liver injury (DILI), but their clinical relevance is unclear.

Methods: We collected serum and liver biopsy samples from 26 patients with DILI. Medical records were reviewed, and Luminex multiplex cytokine assay for 65 serum cytokines was done in those patients. A pathologist performed histologic examinations using the hepatic activity index and immunohistochemistry (IHC) for CD3/CD68/CD38.

Results: 15/26 (57.7%) patients achieved resolution within 30 days after the initial diagnosis. When we divided patients into early resolution (within 30 days, R) and non-resolution (NR) and compared characteristics, the NR group showed higher serum direct bilirubin (DB) and alkaline phosphatase (ALP) levels. Among 65 serum cytokines, CXC motif chemokine ligand 13 (CXCL13) was the only factor that correlate all of the parameters reflecting cholestatic liver injury such as total bilirubin (TB), DB, ALP, and gamma-glutamyl transferase (GGT). We confirmed this cytokine was significantly elevated in DILI patients compared to healthy subjects. Importantly, the NR group showed a significantly higher level of serum CXCL13 compared to the R group (mean 316.4±167.2 vs. 144.3±81.1 pg/mL, v0.002). The high CXCL13 group showed elevated TB, DB, ALP, decreased albumin level, and high albumin-bilirubin (ALBI) score. Higher CXCL13 levels also tended to have severe porto-periportal activity in the liver biopsy samples. Finally, a high CXCL13 level was an indepdent factor associated with the NR in the multivariate analysis (odds ratio=13.57, p=0.039).

Conclusions: These findings suggest that higher serum CXCL13 might be associated with severe cholestatic liver injury in DILI and can be a prognostic marker. Further clinical and mechanistic studies are needed to validate our observation.

Keywords: Drug induced liver injury, CXCL13, Cytokine array, Early resolution

PE-239

The Effect of Turmeric Powder on Liver Enzyme Levels in Male Wistar Rats Induced Hyperlipidemia

Adi Nugraha[1], Muhammad Taufiqurrahman Guretno[1], Rizki Fajar Utami[2], Asri Hendrawati[2]

[1]Faculty of Medicine, Universitas Islam Indonesia, [2]Department of Biochemistry, Faculty of Medicine, Universitas Islam Indonesia

Aims: This study aimed to determine the effect of turmeric powder (Curcuma longa) on *Aspartate Transaminase* (AST) and *Alanine Aminotransferase* (ALT) levels in Male Wistar Rats Induced Hyperlipidemia.

Methods: This research consisted of four groups: the first group (K-) fed with a standard diet (n=5), the second group (K+) induced by hyperlipidemia (n=5), the third group (P1) induced hyperlipidemia plus simvastatin 0.18 mg/200g BW (n=5), the fourth group (P2) induced hyperlipidemia plus turmeric powder 200mg/200g BW (n=5). Two milliliters of quail egg yolk were given for two weeks to induce hyperlipidemia. Cardiac blood plasma were collected to examine the level of AST and ALT. The normal ranges of AST and ALT are 0-35 U/L and 7-56 UL respectively. All data were expressed as mean±SD and analyzed using One-Way ANOVA with a post hoc test. Values

were considered significant at $p<0.05$.

Results: The average AST levels in each group were 36.17 (K-), 69.72 (K+), 38.72 (P1), and 43.82 (P2) U/L. The average ALT levels in each group were 19.01 (K-), 35.05 (K+), 21.36 (P1), and 26.46 (P2) U/L. The results of One-Way ANOVA tests showed that there were significant differences in AST ($p<0.001$) and ALT ($p<0.001$) levels among the groups.

Conclusions: These data confirmed that turmeric powder has significant effect on liver enzymes in wistar rats induce hyperlipidemia.

Keywords: Turmeric, Liver, Enzymes, Hyperlipidemia

PE-240

The Role of M2BPGi for Screening Advanced Hepatic Fibrosis in Elderly Patients

Hoon Gil Jo[1], Mimi Kim[2], Dae Won Jun[3,4], Eileen Yoon[3,4], Se Young Jang[5], Ki Tae Yoon[6,7], Young Youn Cho[8], Yang Hyun Baek[9], Sang Yi Moon[9]

[1]Department of Internal Medicine, Wonkwang University College of Medicine and Hospital, Iksan, South Korea, [2]Department of Radiology, Hanyang University College of Medicine, Seoul, Korea, [3]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea, [4]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, South Korea, [5]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea, [6]Department of Internal Medicine, College of Medicine, Pusan National University, Busan, Korea, [7]Liver Center, Pusan National University Yangsan Hospital, Yangsan, Korea, [8]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea, [9]Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea

Aims: Non-invasive fibrosis markers such as Fibrosis-4 (FIB-4) or NAFLD Fibrosis Score (NFS) are simple and powerful tools to rule out progressive fibrosis in middle age. However, it is known that FIB-4 and NFS showed very low specificity in elderly. The purpose of this study is to determine if Mac-2 binding protein glycan isomer (M2BPGi) and non-invasive test (NIT) and their combination could be helpful in diagnosing advanced liver fibrosis in elderly patients aged ≥65 years.

Methods: Of the 2,177 patients who visited the gastroenterology department of six tertiary general hospitals and performed M2BPGi and transient elastography test (TE), 521 elderly patients aged 65 years or older were finally analyzed. FIB-4 and NFS were calculated for all subjects. Progressive fibrosis was defined as a TE ≥ 8.0 kPa.

Results: A total of 521 elderly patients were included, with an average age of 74.1±5.3 years. Based on the FIB-4 cut-off value 2.0, the sensitivity and specificity for screening advanced hepatic fibrosis were 90.4% and 45.2%. When the M2BPGi cut-off value was set as 0.8, the sensitivity and specificity in the elderly patients were 83.9% and 38.8%, respectively. The sequential combination of FIB-4 and M2BPGi showed 77.1%, 62.1%, 54.0%, and 82.5% of sensitivity, specificity, positive predictive value, and negative predictive value, respectively. In the case of using the sequential combination of FIB-4 and M2BPGi, the unnecessary referral rate for transient elastography examination in elderly patients was reduced by 24.7% compared to the case of using FIB-4 alone.

Conclusions: The sequential combination of FIB-4 followed by M2BPGi can reduce the false positive rate in elderly patients with mild fibrosis. Therefore, it could reduce unnecessary additional investigations.

Keywords: M2BPGi, Elderly patient, FIB-4

PE-241

Utilizing Data Mining Techniques to Develop Accurate Classification Models for Hepatitis C Virus Infection Diagnosis

Rifaldy Fajar[1], Xera Caroline[2], Laura Beatrix[2], Marco Beccheti[1]

[1]Department of Mathematics and Computer Science, Karlstad University, Sweden, [2]Bioinformatics Research Laboratory, Karlstad University, Sweden

Aims: Globally, an estimated 58 million people have chronic hepatitis C virus infection, with about 1.5 million new infections occurring per year. Consequently, developing accurate prediction models using machine learning techniques holds immense value. This study aimed to leverage the power of data mining to classify patients suspected of having HCV infection using various classification models.

Methods: We leveraged a diverse and extensive dataset obtained from the University of California, Irvine (UCI) Machine Learning Repository. This dataset encompassed a rich array of clinical and demographic information concerning patients under suspicion of HCV infection. By integrating this vast and heterogeneous dataset, we aimed to construct classification models that would encapsulate the intricate dimensions of HCV infection. Advanced data mining techniques, including Logistic Regression (LR), k-Nearest Neighbors (KNN), Decision Trees (DT), Support Vector Machines (SVM), Gaussian Naive Bayes (NB), and Random Forest (RF), were employed to develop and evaluate the effectiveness of the models.

Results: Our findings highlighted the exceptional performance of the Random Forest (RF) classifier, surpassing all other methods investigated in this study. The RF classifier exhibited an impressive accuracy rate of 97.3%, demonstrating its capability to accurately classify patients suspected of HCV infection. Furthermore, the area under the curve (AUC) values for the LR, KNN, DT, SVM, Gaussian NB, and RF models were found to be 0.931, 0.973, 0.954, 0.973, 0.897, and 0.997, respectively. Notably, the RF model yielded the highest AUC, underscoring its superior predictive performance.

Conclusions: By unleashing the potential of data mining techniques on the extensive dataset sourced from the University of California, Irvine (UCI) Machine Learning Repository, we successfully developed a robust and accurate model for classifying patients suspected of having HCV infection. The remarkable performance of the Random Forest classifier highlights its significance as a valuable tool for healthcare professionals, empowering them to achieve precise and timely diagnoses of HCV. These findings illuminate the transformative role of data mining in enhancing diagnostic capabilities for HCV infection, thereby contributing to improved patient outcomes. Future research endeavors should focus on incorporating larger and more diverse datasets, enabling the generalizability and applicability of these models to advance HCV management and healthcare delivery.

Keywords: Hepatitis C virus (HCV) infection, Multi-omics data, Gene regulatory networks, Therapeutic targets

PE-242

Empowering Community Health Workers to Enhance Hepatitis Management in Underprivileged Families: A Community-Based Intervention in East Java, Indonesia

Sahnaz Vivinda Putri, Sinta Amalia, Pia Wulandari, Hermansyah Markonah dan Tatiana Betril Mubin

Health Management Laboratory, International University Semen Indonesia, Indonesia

Aims: Hepatitis remains a significant health concern, particularly among underprivileged families in resource-limited settings. In East Java, Indonesia, where approximately 11% of the population is classified as poor, these families face specific challenges in accessing and managing hepatitis. This study aimed to evaluate the impact of a community-based intervention that empowered trained community health workers (CHWs) to improve hepatitis management among these underprivileged families.

Methods: A pre-post-intervention study design was employed. In collaboration with local healthcare authorities, CHWs were selected from within the target communities and underwent comprehensive training on hepatitis prevention, diagnosis, and management. The intervention comprised three main components: (1) community awareness campaigns, (2) capacity building of CHWs, and (3) strengthening healthcare infrastructure. Baseline and post-intervention assessments were conducted to measure changes in knowledge, testing rates, treatment adherence, and the overall burden of hepatitis in the target population.

Results: A total of 600 individuals from underprivileged families in East Java participated in the study. The baseline assessment revealed low levels of hepatitis knowledge and limited access to healthcare services, with only 12% of participants reporting previous testing. Following the intervention, significant improvements were observed in knowledge levels, with a post-intervention increase to 76% ($p<0.001$). Hepatitis testing rates increased dramatically, with 65% of participants reporting having undergone testing ($p<0.001$). Moreover, treatment adherence among diagnosed cases improved to 82% ($p<0.001$). The overall hepatitis burden in the target population decreased by 35%, indicating the intervention's positive impact.

Conclusions: This community-based intervention, leveraging trained CHWs, demonstrated a remarkable impact on hepatitis management among underprivileged families in East Java, Indonesia. By empowering CHWs and fostering community engagement, the intervention effectively addressed knowledge gaps, increased testing rates, and enhanced treatment adherence. The findings underscore the importance of utilizing community-based resources and strengthening healthcare infrastructure to improve hepatitis outcomes in resource-constrained settings. Scaling up similar interventions holds promise for reducing the burden of hepatitis and promoting health equity in vulnerable populations. Policymakers and healthcare stakeholders should prioritize the integration of CHWs within the healthcare system to optimize hepatitis management in underprivileged communities.

Keywords: Hepatitis, Community-based intervention, Underprivileged families, Community health workers (CHWs)

PE-243

Gemigliptin Alleviates Succinate Induced Endoplasmic Reticulum Stress and Activation of Hepatic Stellate Cells

Dinh-Vinh Do, Giang Nguyen, So Young Park, Eun-Hee Cho*, Dae Hee Choi*

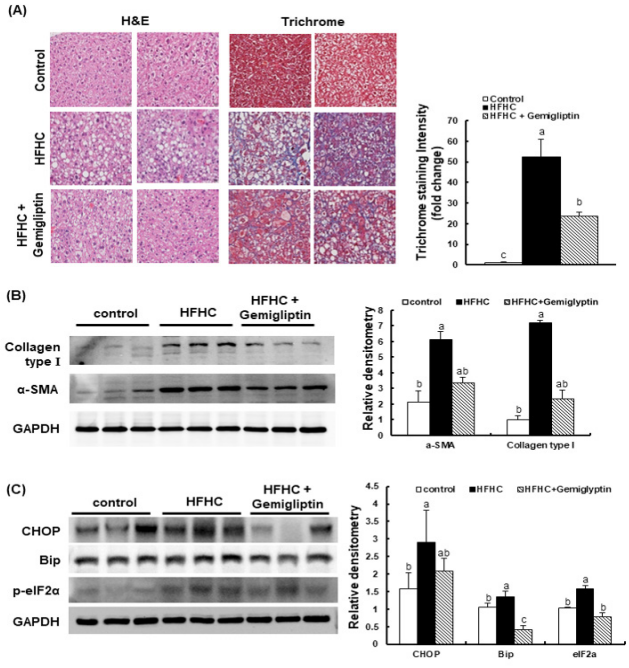
Department of Internal Medicine, School of Medicine, Kangwon National University, Republic of Korea

Aims: Hepatic stellate cells (HSCs) activation is the principal event in the development of liver fibrosis in which succinate-GPR91 signaling has recently been shown to be a contributor. Moreover, endoplasmic reticulum (ER) stress has been reported to involve in HSC activation, but its association with succinate in pathogenesis of liver fibrosis remains scarce. In this study, we investigated the role of gemigliptin, an antidiabetic dipeptidyl peptidase (DPP)-4 inhibitor, in the succinate-induced ER stress and activation of HSCs.

Methods: LX-2 cells, the immortalized human HSCs, were treated with succinate and gemigliptin. For animal experiments, C57BL/6N mice were divided into 3 groups: control diet, high-fat high-cholesterol (HFHC) diet, and HFHC diet mixed with gemigliptin.

Results: Succinate significantly induced HSC activation and increased expression of inflammatory markers and the increase in the migration of HSCs. The treatment of succinate also caused ER dilation and activated the unfolded protein response (UPR) signaling as PERK, eIF2alpha, Bip, suggesting increasing ER stress in HSCs. All responses of HSCs to succinate were attenuated with the co-treatment of gemigliptin. Moreover, the exposure of HSCs to tunicamycin, an inducer of ER stress, promoted the expression of α-SMA, proliferation and migration of HSCs. *In vivo*, the level of fibrotic and ER stress markers was increased in mice fed with HFHC diet and the administration of gemigliptin improved these changes in HFHC-induced mice (Figure 1).

Figure 1 .



Conclusions: This study showed the involvement of ER stress in the activation of succinate-induced LX-2 HSCs and gemigliptin significantly reduced ER stress in HSC activation. Therefore, gemigliptin may become an anti-fibrotic agent and targeting to succinate and ER stress may be a promising therapeutic in the management of liver fibrosis.

Keywords: Succinate, Hepatic stellate cells, Endoplasmic reticulum stress, Gemigliptin, Liver fibrosis

PE-244

Is It True That Reliogiosity Increases Survival Rate in Patients with Liver Failure?

Lintong H Simbolon[1], Rosinta H P Purba[2], Helen Try Juniasti[3], Ester Marnita Purba[4]

[1]Department of Law, University of Lampung, Lampung, Indonesia, [2]Department of Economics, Learning-Up Institute, Yogyakarta, Indonesia, [3]Department of Public Health, Cendrawasih University, Papua, Indonesia, [4]Department of Industrial Engineering, Widyamataram University, Yogyakarta, Indonesia

Aims: Recent research has established the multifaceted features of religious involvement and evaluated how religious variables interact with diverse biobehavioral and psychosocial constructs to determine health status by suggested pathways linking religion and health. However, research on how the religiosity concept is associated with improved survival in liver failure patients remains unclear. This study aims to determine the characteristics of religiosity on the mental health quality of liver failure patients to increase survival rates.

Methods: This study used a reputable published journal (PubMed/Medline, Scopus) with the following criteria, which were published in the last 10 years from 2011 to 2021, and using a questionnaire developed by Tix and Frazier (1998). Of several journals collected, 11 (eleven) articles were selected.

Results: The study found that liver failure candidates with high religious coping (defined as having faith in God, trusting in God, seeking God's help, trying to perceive God's will in the disease, and worship or religious activities) have more pro-longed posttransplant survival than those with low religiosity. Patients with a negative score for the "seeking for God factor" were younger, but they had a three-fold increased risk of mortality from all causes compared to those with positive scores. Religiosity appears to be a coping mechanism for these people as they face the challenges of their new health problems. Further, it becomes median to mitigate mental health problems with lower levels of depression, higher rates of hope, and well-being. Further, it promotes lower patient mortality, including post-liver transplant patients, improved drug adherence, and better health behaviors.

Conclusions: In conclusion, in patients with kidney failure, religion is attributed to prolonged survival rates. It's critical to emphasize how important it is for the care team to include religiosity as a disease-coping mechanism. Active coping, social support, and a multidisciplinary section may attempt transplanted patients to have an improved clinical outcome.

Keywords: Religiosity, Coping mechanism, Prolonged survival, Mental health

PE-245

Increased Risk of Osteoporotic Fracture in Patients with Autoimmune Hepatitis

Jihye Lim[1], Ye-Jee Kim[2], Seonok Kim[2], Jonggi Choi[3]

Division ofGastroenterology and Hepatology, Department ofInternal Medicine, Yeouido St. Mary's Hospital, College ofMedicine, The Catholic University of Korea, Seoul, Korea[1]; Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea[2]; Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea[3]

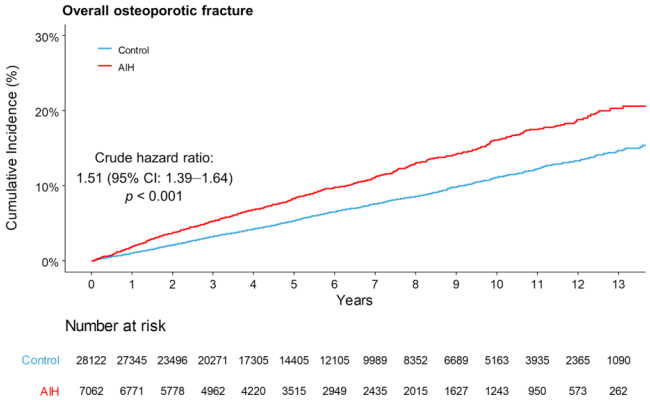
Aims: Few large-scale studies have been published regarding the association between autoimmune hepatitis (AIH) and risk of osteoporotic fracture. This study aimed to determine the risk of developing an osteoporotic fracture in patients with AIH.

Methods: We used claims data from the Korean National Health Insurance Service between 2007 and 2020. Patients with AIH (n 5 7,062) were matched with controls (n 5 28,122) based on age, sex, and duration of follow-up using a ratio of 1:4. Osteoporotic fractures included fractures of the vertebrae, hip, distal radius, and proximal humerus. The incidence rate (IR) and IR ratio of osteoporotic fracture were compared between the 2 groups, and their associated factors were evaluated.

Results: During a median follow-up period of 5.4 years, 712 osteoporotic fractures occurred in patients with AIH with an IR of 17.5 per 1,000 person-years. Patients with AIH had a significantly higher risk of osteoporotic fractures than matched controls, with an IR ratio of 1.24 (95% confidence intervals, 1.10–1.39, $p<0.01$) in the multivariable analysis. Female sex, older age, history of stroke, presence of cirrhosis, and use of glucocorticoids were associated with an increased risk of osteoporotic fractures. In the 2-year landmark analysis, longer duration of glucocorticoid exposure was associated with an incremental increased risk of osteoporotic fracture.

Conclusions: Patients with AIH had an increased risk of osteoporotic fracture compared with controls. The presence of cirrhosis and long-term use of glucocorticoids further adversely affected osteoporotic fracture in patients with AIH.

Keywords: Autoimmune hepatitis, Osteoporosis, Fracture, Glucocorticoid



PE-246

Serum CCL4 as a Prognostic Biomarker for Drug-Induced Liver Injury

Hee Sun Cho[1,2], Jae-Sung Yoo[1,2], Ji Hoon Kim[1,2], Ji Won Han[1,2], Hyun Yang[1,2], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Pil Soo Sung[1,2*]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, 06591, Republic of Korea, [2]Division of Gastroenterology and Hepatology, Department of Internal medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, 06591, Republic of Korea

Aims: Current studies introduce serum chemokines upregulated in drug-induced liver injury (DILI), but the clinical relevance with the disease status is not well understood. CCL4 is reported to be related with severe liver injury in acute hepatitis A, but it's correlation with DILI and clinical liver injury requires further investigation.

Methods: We collected serum and liver biopsy samples from 26 patients with DILI. Medical records were reviewed, and Luminex multiplex cytokine assay for 65 serum cytokines was done in those patients. A pathologist performed histologic examinations using the hepatic activity index and immunohistochemistry (IHC) for CD3/CD20/CD68/CD38.

Results: Among 26 patients, 15 patients (57.7%) achieved resolution within 30 days after the initial diagnosis of DILI. Accordingly, patients were divided into two groups, resolution within 30 days (R) and non-resolution within 30 days (NR). Comparing liver biochemistries, including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (rGTP), total bilirubin (TB), direct bilirubin (DB), albumin and the international normalized ratio (INR), NR group showed higher level of serum TB, DB, ALP, and decreased level of serum albumin. NR group showed significant elevation of serum CCL4 than R group (mean 119.1±18.4, 68.2±9.6, respectively, p=0.018). There were significant elevation of TB, DB, ALP and reduction of albumin in patients with elevated serum CCL4. ALBI score, an index of the severity of liver dysfunction, also increased in proportion to serum CCL4 level. Liver biopsy results of lobular activity, portal-periportal activity, fibrosis, and immunohistochemistry (CD3, CD20, CD38, CD68) was not related with serum CCL4 level. With univariate and multivariate analysis, high level of CCL4 showed significant risk of liver damage.

Conclusions: Serum CCL4 is associated with liver dysfunction in DILI. Its potency as a prognostic marker for DILI patient should be more invegistated in clinical studies with larger population.

Keywords: DILI, Prognostic biomarker

PE-247

Metabolic Disorders Are Associated with Drug-Induced Liver Injury during Anti-Tuberculosis Treatment

Kyeong Ah Jang[1], Jihye Lim[1], Jinsoo Min[2], Tae Joon An[3]

[1]Division of Gastroenterology and Hepatology,Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, [2]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Drug-induced liver injury (DILI) poses a significant obstacle leading to discontinuation of anti-tuberculosis (TB) treatment (ATT). Some studies have suggested that metabolic disorders may increase the risk of DILI during ATT. This study aimed to identify the risk factors of DILI, particularly metabolic disorders, during ATT.

Methods: A multicenter prospective observational cohort study for evaluating the adverse event during ATT was carried out in Korea from 2019 to 2021. Drug-susceptible TB patients treated with standard ATT for 6 months were included. They were divided into two groups depending on the presence of one or more metabolic conditions, such as insulin resistance, hypertension, obesity, and dyslipidemia. We monitored ATT-related adverse events, including DILI as well as treatment outcome. The incidence of DILI was compared between individuals with and without metabolic disorders, and related factors were evaluated.

Results: Of 684 patients, 52 (7.6%) experienced DILI, and 92.9% of them had metabolic disorders. In the multivariable analyses, underlying metabolic disorders (adjusted hazard ratio [aHR]: 2.85; 95% CI: 1.01-8.07) and lower serum albumin than 3.5 g/dL (aHR: 2.26, 95% CI:1.29-3.96) were risk factors of DILI during ATT. In the one-month landmark analyses, metabolic disorders were linked to an elevated risk of DILI, especially significant ALT elevation. Treatment outcome was not affected by the presence of metabolic disorders.

Conclusions: Patients with metabolic disorders had an increased risk of ATT-induced liver injury compared to controls. Presence of metabolic disorders and hypoalbuminemia adversely affected liver in patients with ATT.

Keywords: Tuberculosis, Chemical and drug induced liver injury, Metabolic syndrome

PE-248

Gamma-Glutamyl Transferase and Risk of All-Cause and Disease-Specific Mortality in People with Diabetes: A Nationwide Cohort Studyy

Goh Eun Chung[1*], Su-Min Jeong[2*], Su Jong Yu[3], Jeong-Ju Yoo[4], Yuri Cho[5], Kyu-na Lee[6], Dong Wook Shin[2,7], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Kyungdo Han[8§], [§] Eun Ju Cho[3§]

[1]Department of Internal Medicine and Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Republic of Korea, [2]Department of Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [4]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Soonchunhyang University Bucheon Hospital, Gyeonggi-do, Republic of Korea, [5]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Republic of Korea, [6]Department of Biomedicine & Health Science, The Catholic University of Korea, Seoul, Korea, [7]Department of Clinical Research Design and Evaluation/Department of Digital Health, Samsung Advanced Institute for Health Science, [8]Department of Biostatistics, College of Medicine, Soongsil University, Seoul, Republic of Korea

Aims: Little is known about whether gamma-glutamyl transferase (GGT) confers various disease-specific mortality in patients with type 2 diabetes mellitus (DM). We examined the association of serum levels of GGT with all-cause and disease-specific mortality in patients with DM.

Methods: Using the Korean nationwide health screening database, we included 9,687,066 subjects without viral hepatitis or liver cirrhosis who underwent a health examination in 2009. Subjects were classified into three groups by sex-specific quartiles of serum GGT levels. The underlying causes of death were classified by 10th Revision of the International Classification of Diseases codes. Cox proportional hazards regression analysis was performed.

Results: During the median follow-up period of 8.1 years, 222,242 deaths were identified. All-cause mortality increased as serum GGT levels became higher (hazard ratio [HR], 95% confidence interval [CI]: 1.57, 1.55– 1.59 in the highest GGT quartile compared the lowest GGT quartile (p for trend <0.001). Similar trends were observed for cardiovascular disease (HR, 95% CI: 157, 1.53-1.62), ischemic heart disease (HR, 95% CI: 1.40, 1.33-1.48), and stroke (HR, 95% CI: 1.72, 1.60-1.85) in the highest GGT quartile compared to the lowest GGT quartile (p for trend <0.001). Cancer, liver disease, respiratory disease, and infectious disease - related mortality increased as the quartiles of GGT become higher (cancer: HR=1.56, 95% CI=1.52-1.60, liver-disease: HR=9.42, 95% CI=8.81-10.07, respiratory disease: HR=1.55, 95% CI=1.49-1.62, and infectious disease: HR=1.73, 95% CI=1.59-1.87) in the highest GGT quartile compared to the lowest GGT quartile (p for trend <0.001).

Conclusions: Serum GGT levels may be useful for risk assessment of all-cause and disease-specific mortality among patients with type 2 diabetes.

Keywords: Gamma-glutamyl transferase, Diabetes mellitus, Mortality

PE-249

A Case of Successful Hemostasis of Rectal Variceal Bleeding with Coil Embolization

Deoksu Lee[1], Ju-Yeon Cho[1,2]

[1]Department of Internal Medicine, Chosun University Hospital, [2]Department of Internal Medicine, Chosun University, College of Medicine

Aims: Gastrointestinal varices are associated with cirrhosis and portal hypertension. Variceal hemorrhage is a major cause of morbidity and mortality, with esophageal and gastric varices as the most common source. We report cases of ectopic variceal bleeding, a duodenal varix and rectal varix, presenting as a cause of severe gastrointestinal bleeding.

Methods: A 68-year-old male was admitted to our hospital with about 500cc of hematochezia on the day of admission. The patient had a history of alcoholic liver cirrhosis with previously diagnosed esophageal and gastric varices. Emergency esophagogastroduodenoscopy was done to evaluate for the focus of the bleeding site. Although both esophageal and gastric varices were present, an active stigamata was not noticed. Simoidoscopy to evaluate for the cause of the hematochezia was underwent and revealed a large sized veous distension with multiple red cherry signs.

Results: Variceal ligation was done at the white nipple spots and hemostasis was achieved during the procedure. However, recurrent hematochezia was noted on the following day. Angiography of the rectal varix revealed active bleeding from the superior rectal veins. Hemostasis was achieved through coiling of the bleeding vessel.

Conclusions: Radiological coil embolization should be considered in cases of uncontrollable ectopic variceal bleeding.

Keywords: Liver cirrhosis, Variceal bleeding

PE-250

The Effect of MELD 3.0 Score on the Disparities between Patients with and without Hepatocellular Carcinoma in Korea

Kunhee Kim[1], Deok-Gie Kim[2], Jae Geun Lee[2], Dong Jin Joo[2] and Hye Won Lee[1,3,4]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Departmennt of Surgery, Institute for Transplantation, Yonsei University College of Medicine, Seoul, Korea; [3]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: The Model for End-Stage Liver Disease (MELD) 3.0 has recently been suggested for determining liver allocation. We aimed to apply MELD 3.0 to a Korean population, and to discover differences between patients with and without hepatocellular carcinoma (HCC).

Methods: This was a retrospective study that included 2,203 patients diagnosed with liver cirrhosis at Severance Hospital between 2016 and 2022. Harrell's concordance index was used to validate the ability of MELD scores to predict 90-day survival.

Results: During a mean follow-up of 12.9 months, 90-day survival was 61.9% in all patients, 50.4% in the HCC group, and 74.8% in the non-HCC group. Within the HCC group, the concordance index for patients on the waitlist was 0.653 using MELD, which increased to 0.753 using MELD 3.0. Among waitlisted patients, the 90-day survival of HCC patients was worse than that of non-HCC patients with MELD scores of 31–37 only (69.7 vs 30.0%, v0.001). Applying MELD 3.0, the 90-day survival of HCC patients was worse than that of non-HCC patients across a wider range of MELD 3.0 scores compared to MELD, with MELD 3.0 scores of 21-30 and 31-37 (82.0 vs 72.5% and 72.3% vs 24.3%, p=0.02 and <0.001, respectively).

Conclusions: MELD 3.0 predicted 90-day survival of the HCC group more accurately than did the original MELD score, but the disparity between HCC and non-HCC patients increased, particularly in patients with MELD scores of 21-30. Therefore, a novel exception score is needed or current exception score system should be modified.

Keywords: MELD score, MELD 3.0, Liver cirrhosis, Hepatocellular carcinoma

PE-251

Personalized Antiviral Drug Selection in Chronic Hepatitis B Patients Using a Machine Learning Model: A Multinational Study

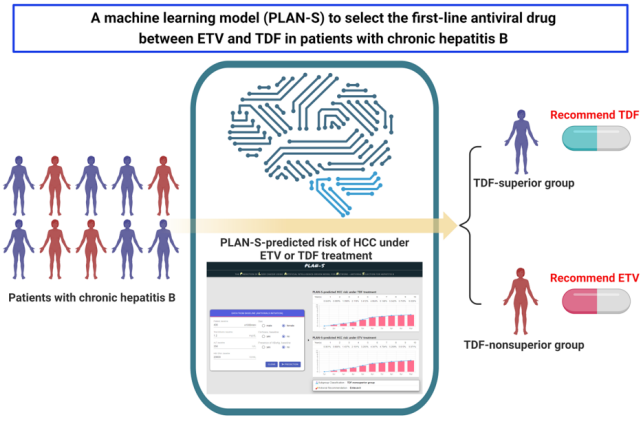
Moon Haeng Hur[1],*, Min Kyung Park[1],*, Terry Cheuk-Fung Yip[2],*, Chien-Hung Chen[3],*, Hyung-Chul Lee[4],*, Won-Mook Choi[5],*, Seung Up Kim[6], Young-Suk Lim[5], Soo Young Park[7], Grace Lai-Hung Wong[2], Dong Hyun Sinn[8], Young-Joo Jin[9], Sung Eun Kim[10], Cheng-Yuan Peng[11], Hyun Phil Shin[12], Chi-Yi Chen[13], Hwi Young Kim[14], Han Ah Lee[14], Yeon Seok Seo[15], Dae Won Jun[16], Eileen L. Yoon[16,17], Joo Hyun Sohn[18], Sang Bong Ahn[19], Jae-Jun Shim[20], Soung Won Jeong[21], Yong Kyun Cho[22], Hyoung Su Kim[23], Myoung-jin Jang[24], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [2]Medical Data Analytics Centre (MDAC), Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China, [3]Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, [4]Department of Anesthesiology, Seoul National University College of Medicine, Seoul, Republic of Korea, [5]Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea, [6]Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, [7]Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Republic of Korea, [8]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [9]Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, Republic of Korea, [10]Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea, [11]Center for Digestive Medicine, Department of Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan, [12]Department of Gastroenterology and Hepatology, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Republic of Korea, [13]Division of Hepatogastroenterology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan, [14]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea, [15]Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Republic of Korea, [16]Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Republic of Korea, [17]Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea, [18]Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Republic of Korea, [19]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University College of Medicine, Seoul, Republic of Korea, [20]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Republic of Korea, [21]Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea, [22]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [23]Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea, [24]Medical Research Collaboration Center, Seoul National University Hospital, Seoul, Republic of Korea

Aims: Tenofovir disoproxil fumarate (TDF) is reportedly superior or at least comparable to entecavir (ETV) for the prevention of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients; however, it has distinct long-term renal and bone toxicities. This study aimed to develop and validate a machine learning model (designated as PLAN-S) to predict an individualized risk of HCC during ETV or TDF therapy.

Methods: This multinational study included 13,970 CHB patients. The derivation (n=6,790), Korean validation (n=4,543), and Hong Kong–Taiwan validation cohorts (n=2,637) were established. Patients were classified as the TDF-superior group when a PLAN-S-predicted HCC risk under ETV treatment is greater than under TDF treatment, and the others were defined as the TDF-nonsuperior group.

Results: The PLAN-S model was derived using eight variables and generated a c-index between 0.67 and 0.78 for each cohort. The TDF-superior group included a higher proportion of male and cirrhotic patients than the TDF-nonsuperior group. In the derivation, Korean validation, and Hong Kong–Taiwan validation cohorts, 65.3%, 63.5%, and 76.4% of patients were classified as the TDF-superior group, respectively. In the TDF-superior group of each cohort, TDF was associated with a significantly lower risk of HCC than ETV (hazard ratio=0.60–0.73, all p<0.05). In the TDF-nonsuperior group, however, there was no significant difference between the two drugs (hazard ratio=1.16–1.29, all P>0.1).



Conclusions: Considering the individual HCC risk predicted by PLAN-S and the potential TDF-related toxicities, TDF and ETV treatment may be recommended for the TDF-superior and TDF-nonsuperior groups, respectively (Figure).

Keywords: Liver cancer, Antiviral selection, Deep neural networking, Random survival forests

PE-252

Extrahepatic Malignancies and Antiviral Drugs for Chronic Hepatitis B: A Nationwide Cohort Study

Moon Haeng Hur[1,*], Dong Hyeon Lee[1,2*], Jeong-Hoon Lee[1], Mi-Sook Kim[3], Jeayeon Park[1], Hyunjae Shin[1], Sung Won Chung[1], Hee Jin Cho[1], Min Kyung Park[1], Heejoon Jang[2], Yun Bin Lee[1], Su Jong Yu[1], Won Kim[2], Yong Jin Jung[2], Yoon Jun Kim[1], Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea, [3]Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea

Aims: Many previous studies comparing tenofovir disoproxil fumarate (TDF) and entecavir (ETV) reported that TDF is superior, or at

least comparable, to ETV in terms of hepatocellular carcinoma prevention in patients with chronic hepatitis B (CHB). In addition, our recent study suggested that CHB is associated with an increased risk of extrahepatic malignancy (EHM), which normalized with antiviral treatment. We aimed to compare the risk of EHM as well as intrahepatic malignancy (IHM) associated with ETV versus TDF.

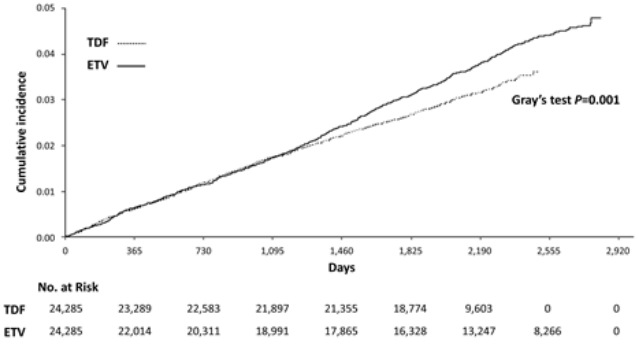
Methods: Based on claims data of the National Health Insurance Service of Korea, this nationwide cohort study included treatment-naïve CHB patients who initiated antiviral therapy either with ETV (ETV group: n=24,287) or with TDF (TDF group: n=29,199) between 2012 and 2014. The primary outcome was the development of any primary EHM. Secondary outcomes were the development of the 10 most prevalent EHMs in Korea and overall IHM.

Results: During median follow-up of 5.9 years, 822 (3.4%) and 706 (2.9%) patients in the ETV and TDF groups, respectively, developed EHM. EHM incidence rate differed significantly between within 3 years and beyond 3 years in both groups (both $p<0.01$, Davies test). During the first 3 years, there was no difference in EHM risk between groups in the propensity score-matched cohort (subdistribution hazard ratio [SHR]=1.01, 95% confidence interval [CI]=0.88–1.17, $p=0.84$). After year 3, however, TDF was associated with a significantly lower EHM incidence, compared to ETV (SHR=0.70, 95% CI=0.60–0.81, $p<0.01$; Figure). Various sensitivity and subgroup analyses reproduced these results. The TDF group showed a significantly lower incidence of stomach cancer (SHR=0.57), breast cancer (SHR=0.53), and non-Hodgkin lymphoma (SHR=0.34) than the ETV group after 3 years. Regarding the incidence of IHM, the superiority of TDF over ETV was maintained both before year 3 (SHR=0.88, 95% CI=0.81–0.95, $p<0.01$) and after year 3 (SHR=0.68, 95% CI=0.62–0.75, $p<0.01$), with the latter being more prominent.

Conclusions: TDF was associated with about 30% lower risk of EHM as well as IHM than ETV in CHB patients after 3 years of antiviral therapy.

Keywords: Non-liver cancer, Hepatitis B virus, Tenofovir, Entecavir

Figure.



PE-253

Comparison of First-Line Systemic Therapies for Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Moon Haeng Hur, Hyunjae Shin, Jeayeon Park, Ju Yeon Kim, Sung Won Chung, Yun Bin Lee, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

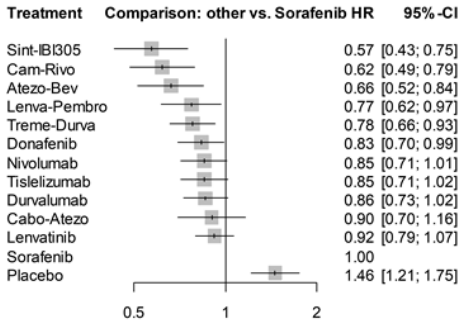
Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

Aims: Recently, several novel systemic therapies and their combinations have shown favorable outcomes in patients with advanced hepatocellular carcinoma (HCC). We performed a systemic review and network meta-analysis (NMA) to compare the efficacies of these treatments in relation to the current standards of care.

Methods: A systematic literature search was conducted from inception to December 2022 on PubMed, EMBASE, Web of Science, and the Cochrane Controlled Register of Trials to identify phase III randomized controlled trials assessing the efficacy of systemic agents used as first-line therapies among patients with unresectable HCC. Studies investigating locoregional treatment or conventional cytotoxic chemotherapy were excluded. To focus on recently introduced systemic therapies, treatment regimens presented prior to 2018 (i.e., the year of lenvatinib introduction) were also excluded, except for sorafenib. Hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS) were pooled and *P* score was calculated to rank treatment regimens.

Results: A total of 5,038 studies were identified after duplicates removal and 12 trials (13 regimens) were included for NMA. Low level of heterogeneity ($I2=0\%$) and inconsistency (Cochran's $Q=0.01$, $p=0.94$) was confirmed. Compared to sorafenib, sintilimab plus a bevacizumab biosimilar (Sint-IBI305) showed the greatest OS benefit (HR=0.57, 95% CI=0.43–0.75, *P* score=0.944), followed by camrelizumab-rivoceranib (Cam-Rivo; HR=0.62, 95% CI=0.49–0.79, *P* score=0.892) and atezolizumab-bevacizumab (Atezo-Bev; HR=0.66, 95% CI=0.52–0.84, *P* score=0.834; Figure). The superiority of Sint-IBI305 was maintained in the subgroup of HCC with macrovascular invasion and/or extrahepatic spread and hepatitis B virus-related HCC. Regarding PFS, Cam-Rivo ranked first (HR=0.52, 95% CI=0.41–0.65, *P* score=0.927), followed by Sint-IBI305 (HR=0.56, 95% CI=0.45–0.69, *P* score=0.863) and lenvatinib-pembrolizumab (Lenva-Pembro; HR=0.57, 95% CI=0.46–0.72, *P* score=0.848).

Figure.



Conclusions: Novel systemic therapies including Sint-IBI305 and Cam-Rivo demonstrated promising results compared to the current standard regimens (sorafenib, lenvatinib, and Atezo-Bev); however, further validation is warranted.

Keywords: Liver cancer, Unresectable, Systemic treatment, Immunotherapy

PE-254

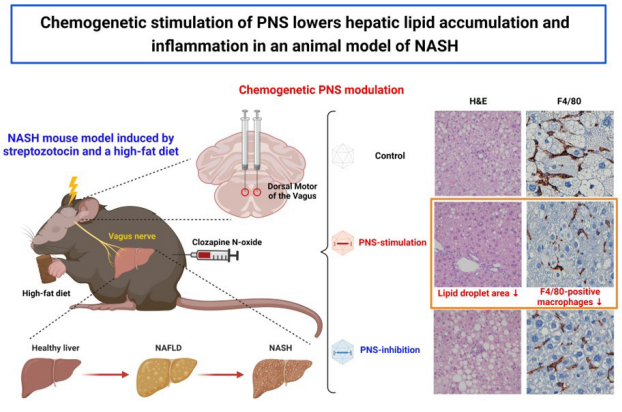
Chemogenetic Stimulation of the Parasympathetic Nervous System Lowers Hepatic Lipid Accumulation and Inflammation in a Non-Alcoholic Steatohepatitis Mouse Model

Moon Haeng Hur[1,2,*], Woojin Song[2,*], Deokhyeon Cheon[2,*], Young Chang[3], Young Youn Cho[4], Yun Bin Lee[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Hyung Jin Choi[2,†], Cherl NamKoong[2,†], Jeong-Hoon Lee[1,†]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [2]Department of Anatomy and Cell Biology, Department of Biomedical Sciences, Neuroscience Research Institute, and Wide River Institute of Immunology, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Department of Internal Medicine, Digestive Disease Center, Institute for Digestive Research, Soonchunhyang University College of Medicine, Seoul, Republic of Korea, [4]Department of Internal Medicine, Chung Ang University College of Medicine, Seoul, Republic of Korea

Aims: The role of the parasympathetic nervous system (PNS) in the pathogenesis of nonalcoholic steatohepatitis (NASH) is largely unknown. In this study, the effect of PNS modulation on NASH was investigated using chemogenetics.

Methods: A streptozotocin (STZ) and high-fat diet (HFD)-induced NASH mouse model was used. To activate or inhibit the PNS, chemogenetic human M3-muscarinic receptor coupled with either Gq or Gi protein-containing viruses was injected into the dorsal motor nucleus of the vagus at week 4 and clozapine N-oxide was administered intraperitoneally for a week from week 11. Three groups (PNS-stimulation, PNS-inhibition, and control) were compared in terms of heart rate variability (HRV), histological lipid droplet area, nonalcoholic fatty liver disease activity score (NAS), the area of F4/80-positive macrophages, and biochemical responses.



Results: The STZ/HFD-treated mouse model showed typical histological characteristics of NASH. HRV analysis confirmed that PNS-stimulation and PNS-inhibition groups had significantly higher and lower PNS activity, respectively (both $p<0.05$). The PNS-stimulation group showed a significantly smaller hepatic lipid droplet area (14.3% vs. 20.6%, $p=0.02$) and lower NAS (5.2 vs. 6.3, $p=0.047$) than the control group. The area of F4/80-positive macrophages was significantly smaller in the PNS-stimulation group than in the control group (4.1% vs. 5.6%, $p=0.04$). The PNS-stimulation group showed a lower serum aspartate aminotransferase level than the control group (119.0 vs. 356.0 U/L, $p=0.04$).

Conclusions: In STZ/HFD-treated mice, chemogenetic stimulation of the PNS significantly reduced hepatic fat accumulation and inflammation. The hepatic PNS may play a pivotal role in the pathogenesis of NASH (Figure).

Keywords: Brain-liver axis, Autonomic nervous system, Chemogenetics, Fatty liver

PE-255

Morphological Architectures of Patient-Derived Hepatocellular Carcinoma Organoids with GSK3-Beta Expression Dependent Variability according to Lenvatinib Resistance

Kyungioo Cho[1], Hye Won Lee[1,3,4], Hye Jung Park[1], Eun Kong Lee[1], Sang Hyun Seo[1,2], Jae Seung Lee[1,3,4], Beom Kyung Kim[1,3,4], Seung Up Kim[1,3,4], Do Young Kim[1,3,4], Sang Hoon Ahn[1,3,4], Hee Seung Lee[3,4], Jun Yong Park[1-4]

[1]Yonsei Liver Center, Severance Hospital, [2]Brain Korea 21 PLUS Project for Medical Science, Yonsei University, [3]Department of Internal Medicine, Yonsei University College of Medicine, [4]Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Aims: Organoid models using patient-derived cancer tissues has allowed a better understanding of human cancer as well as development of precision medicine. We evaluated the potential differential sensitivity of HCC organoids(HCOs) to lenvatinib and analyzed the relationship between the resistance group of lenvatinib and intracellular signaling pathways.

Methods: Patient-derived tumor tissue was digested at 37 °C and mixed with Matrigel. After polymerization of Matrigel, medium was added and changed twice a week. To evaluate whether HCO exhibit different sensitivity to drugs, we tested its sensitivity and analyzed the sensitivity in HCO lines with the difference in gene expression.

Results: We successfully established HCO lines at a 76% success rate, presenting as two different morphological types: solid-type and mixed-type. Heterogeneous morphological features of HCOs exhibited differential gene expression and response to lenvatinib, showing highly expressed EGFR, GSK3-beta and FOXO3 with lower sensitivity to lervatinib in solid type HCOs, compared to mixed type HCOs. To confirm the association of morphological lasification with G5K-bela acivation and lervatinio sensitivity, we generated a rHCO from re-biopsied tissue from a patient with HCC progression after lenvatinib treatment and compared it with the HCO established with first biopsied tissue. Specifically, the lenvatinib-resistant rHCO expressed much lower levels of the inactive form of GSK3-beta and higher levels of the active form of GSK3B compared with the original HCO, sug-

gesting higher GSK3-beta activity and Ki-67 levels in resistant cells. Knockdown of GSK3-beta with selective GSK3-beta inhibitor and siRNA restores sensitivity to lenvatinib in association with GSK3-beta activity and morphological features.

Conclusions: Our work demonstrates the relationship between lenvatinib sensitivity and morphological features with GSK3-beta expression and identifies regulators of GSK3-beta activity as potential novel therapeutic agents for restoring lenvatinib sensitivity.

Keywords: Organoid, GSK3-beta, Lenvatinib, Drug resistance

PE-256

Clusterin Inhibits Liver Inflammation and NLRP3 Inflammasome

Hye-Young Seo, So-Hee Lee, Ji Yeon Park, Min Ju Kim, Jae Seok Hwang, Mi-Kyung Kim, Byoung Kuk Jang

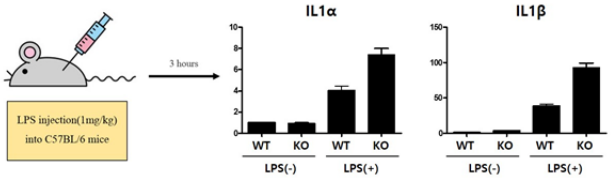
Keimyung University School of Medicine

Aims: Lipopolysaccharide (LPS) is one of the important mechanisms leading to liver inflammation. Elevated LPS in the liver causes hepatocyte damage and stimulates kupffer cells (KC) to activate the NLPR3 inflammasome and IL1β pathways and also release pro-inflammatory cytokines. Clusterin is a glycoprotein involved in cell death, lipid transport and barrier cell protection. However, it is not known whether clusterin is effective for liver inflammation. Here, we investigated the anti-inflammatory effects of clusterin on liver inflammation.

Methods: To study the liver inflammation effect of clusterin, we used a mouse (C57BL/6 or Clusterin knockout) primary KC and primary hepatocyte (HC). Liver inflammation was induced by LPS-injection for 3 h in C57BL/6 or Clusterin knockout mice.

Results: In clusterin knockout mice, LPS injection further increased NLRP3 inflammasome and liver inflammation. LPS-induced inflammatory cytokines were also further increased in clusterin KO primary KC. On the other hand, overexpressed clusterin significantly reduced LPS-stimulated NLRP3 inflammasome pathway by suppressing the expression of NLRP3, caspase1 and IL1β. Clusterin also inhibited inflammatory cytokines including iNOS, IL1α, IL6 and TNFα.

Conclusions: This study shows that loss of clusterin promotes NLRP3 inflammasomes and inflammation, and overexpressed clusterin suppresses NLRP3 and pro-inflammatory cytokines. This suggests that clusterin has anti-inflammatory effects in the liver.



Keywords: Inflammation, Inflammasome, Clusterin, Kupffer cells

PE-257

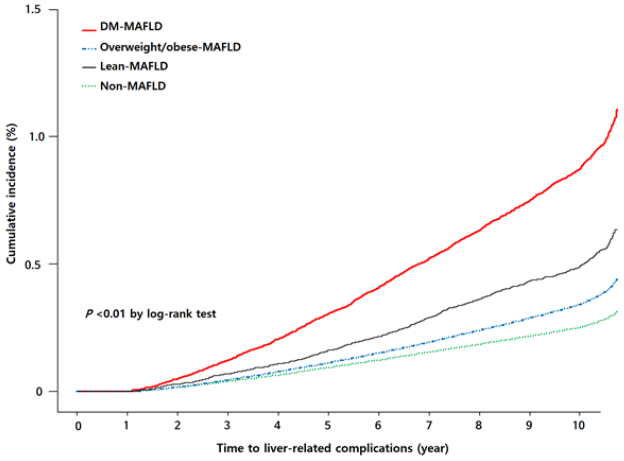
Metabolic Dysfunction–Associated Fatty Liver Disease Is Associated with Increased Risk of Liver-Related Complications: A Nationwide Cohort Study

Hyunjae Shin[1], Min Kyung Park[1], Hye-Sung Moon[2], Sung Won Chung[1], Sungho Won[2,3], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, [2]RexSoft Inc., Seoul 08826, Korea, 3Department of Public Health Sciences, Graduate School of Public Health, Seoul National University, Seoul, South Korea

Aims: Metabolic dysfunction-associated fatty liver disease (MAFLD), a new definition encompassing the entire liver disease associated with metabolic disorders, has been recently proposed. We aimed to analyze the long-term outcome of MAFLD by focusing on liver-related outcomes.

Methods: We analyzed data from the National Health Insurance Service of Korea, including 7,454,412 participants who participated in the health screening program in 2009. MAFLD was defined by an international expert consensus statement previously proposed. Participants were further categorized into four groups followed by the MAFLD definition; non-MAFLD, DM-MAFLD, overweight/obese-MAFLD, and lean-MAFLD. The primary outcome was the development of liver-related complications, including hepatocellular carcinoma, liver transplantation, decompensated liver cirrhosis, and liver-related mortality. The Cox proportional hazard model was used, including adjustment for competing risks.



Results: Of the study subjects, 2,500,080 (33.5%) had MAFLD. During the median follow-up of 10.3 years (interquartile range, 10.1–10.6), 20,843 patients (0.28%) developed liver-related complications. The MAFLD group had a higher overall risk of liver-related complications than the non-MAFLD group (adjusted cause-specific hazard ratio [aCHR]=1.24; 95% confidence interval [CI]=1.21–1.28; p<.001). The DM-MAFLD group showed a significantly higher risk of liver-related complications compared to the non-MAFLD group (aCHR=1.82; 95% CI=1.74–1.91; p<.001), followed by the lean-MAFLD group (aCHR=1.22; 95% CI=1.12–1.33; p<.001), and the overweight/obese-MAFLD group (aCHR=1.13; 95% CI=1.09–1.33; p<.001). Sensitivity analysis after excluding underlying liver disease, the MAFLD group

maintained a significantly higher extrahepatic malignancy than the non-MAFLD group (aCHR=1.28; 95% CI=1.24–1.32; p<.001).

Conclusions: MAFLD is associated with developing liver-related complications. Categorizing MAFLD subgroup according to the positive definition criteria representing the phenotypes of metabolic disorders could help the stratification of the risk of liver-related complications in MAFLD.

Keywords: Metabolic dysfunction-associated fatty liver disease, Liver-related complications, Risk factors

PE-258

Deletion of Mixed Lineage Kinase Domain Like Pseudokinase Aggravate Chronic Alcohol Induced Liver Injury via Increasing Apoptosis

Keon Hwi Im[1*], Waqar Khalid Saeed[2*] Eun Bin Kim[5], A Hyeon Lee[1], Ji Eun Kim[1], Seung Min Lee[1], Xuanyuan hanning[5], Hyun Sung Kim[3], Dae Won Jun[1,5,6], Eileen L. Yoon[5,6]

[1]Department of Translational Medicine, Hanyang University Graduate school of Biomedical Science and Engineering, [2]Department of Biomedical Sciences, Pak-Austria Fachhochschule: Institute of Applied Sciences and Technology, Mang, Haripur, Pakistan, [3]Department of Pathology, and [5]Internal Medicine, Hanyang University School of Medicine, [6]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, Korea

Aims: The mixed lineage kinase domain like pseudokinase (MLKL) is known to play a protective role in non-alcoholic fatty liver disease (NAFLD) via inhibition of necroptosis pathway. However, the role of MLKL in alcoholic liver disease (ALD) is not yet clear.

Methods: C57BL/6N wild-type (WT) and MLKL-knockout (KO) mice (8-10 weeks old) were randomly divided into eight groups. To establish ALD model of different durations ethanol (EtOH) was fed to WT and MLKL KO for 10 days, 4 weeks and 8 weeks. The control group was fed with Lieber-DeCarli control diet for 8 weeks. Mortality, degree of hepatic inflammation, and steatosis were compared among the groups. Bulk mRNA transcriptome analysis was performed. Abundance of transcript and gene expressions were calculated based on read count or Transcript by Million (TPM) value.

Results: Survival rate of MLKL KO mice compared to WT was similar until 4 weeks, but the survival of MLKL KO mice significantly decreased after 8 weeks in ALD model. There was no difference in degree of inflammation, steatosis, and NAS scores between EtOH fed MLKL KO and EtOH fed WT mice at 10 days. However, at 4 weeks and 8 weeks, the degree of hepatic steatosis, NAS and inflammation were increased in MLKL KO mice. RNA transcriptome data showed that fatty acid synthesis, and lipogenesis, mitochondria, and apoptosis related pathways were upregulated in EtOH fed MLKL KO mice compared to EtOH fed WT mice. Although hepatocyte apoptosis (BAX/BCL2 ratio, caspase-3, and TUNEL staining) increased after EtOH intake; however, apoptosis was more significantly increased in EtOH fed MLKL KO mice compared to the WT group. At the same time, hepatic cFLIP was decreased in EtOH fed MLKL KO mice compared to the WT group.

Conclusions: MLKL deletion did not prevent chronic alcohol-induced liver damage independently of necroptosis and exacerbated hepatic steatosis by increasing hepatocyte apoptosis.

Keywords: Mixed lineage kinase domain like pseudokinase, Alcoholic liver disease, Apoptosis, Steatosis

PE-259

Diagnostic Performance of NAFLD Fibrosis Score in Lean NAFLD

Huiyul Park[1§], Eileen L. Yoon[2,3§], Mimi Kim[4], Jonghyun Lee5, Seon Cho[6], Eun-Hee Nah[6*], Dae Won Jun[2,3,5*]

[1]Department of Family Medicine, Myoungji Hospital, Hanyang University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea, [3]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, South Korea, [4]Department of Radiology, Hanyang University College of Medicine, Seoul, Korea, [5]Department of Translational Medicine, Hanyang University Graduate School of Biomedical Science and Engineering, Seoul, Korea, [6]Department of Laboratory Medicine, Health Promotion Research Institute, Seoul, Korea

Aims: Diagnostic performance of fibrosis-4 index (FIB-4) and non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS) for advanced fibrosis in lean patients with NAFLD is limited. We aimed to evaluate the diagnostic performance and current cut-offs of FIB-4 and NFS in individuals with NAFLD.

Methods: This multicenter, retrospective, cross-sectional study analyzed 1,501 patients with biopsy-proven NAFLD. The difference in diagnostic performance of FIB-4 and NFS between lean (body mass index (BMI) <23 kg/m^2) and non-lean (BMI ≥ 23 kg/m^2), and their sensitivity and specificity at the current cut-off value were also evaluated.

Results: Diagnostic performance and area under the receiver operating characteristic curves (AUROCs) of FIB-4 and NFS were comparable between the lean and non-lean groups. The AUROC of FIB-4 and NFS were not different in the lean group (0.807 vs. 0.790). The sensitivity and specificity of the current FIB-4 cut-off values did not change. But, the sensitivity of the current NFS cut-off values was lower in the lean group than in the non-lean group (54.4% vs. 72.7%) (Figure 1). The NFS sensitivity decreased with the BMI quartiles. The FIB-4 sensitivity and specificity did not change according to BMI quartiles.

Conclusions: The overall diagnostic performance (AUROC) of FIB-4 and NFS in diagnosing advanced fibrosis did not differ between the lean and non-lean groups. However, the sensitivity of NFS at the current cut-off value decreased in lean individuals. FIB-4 at the current cut-off value would be a better screening parameter of advanced NAFLD fibrosis in lean individuals.

Keywords: Mixed lineage kinase domain like pseudokinase, Alcoholic liver disease, Apoptosis, Steatosis

PE-260

Tumor Stage Prediction of Hepatocellular Carcinoma Using APG Beads with Graphene Oxide

Tae Hee Lee[1,2], Jiyoon Bu[3,4], Hyuk Soo Eun[5,6,*]

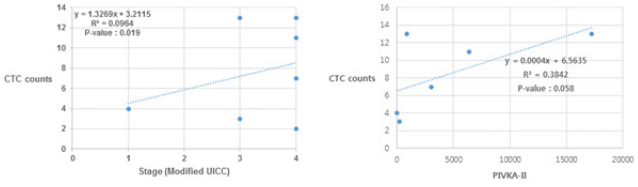
[1]Department of Biomedical Laboratory Science, Daegu Health College, chang-ui building, 15 Yeongsong-ro, Buk-gu, Daegu, 41453, Republic of Korea,

[2]Industry Academic Cooperation Foundation, Daegu Health College, 15 Yeongsong-ro, Buk-gu, Daegu, 41453, Republic of Korea, [3]Department of Biological Sciences and Bioengineering, Inha University, 100 Inha-ro, Michuhol-gu, Incheon, 22212 Republic of Korea, [4]Industry-Academia Interactive R&E Center for Bioprocess Innovation, Inha University, [5]Department of Internal Medicine, Chungnam National University Hospital, 282, Daejeon, Republic of Korea, [6]Department of Internal Medicine, College of Medicine, Chungnam National University, 266, Munwha-ro, jung-gu, Daejeon 35015, South Korea

Aims: It could be expected a good prognosis for patients with hepatocellular carcinoma (HCC) if it is diagnosed at an early stage and treated at an early stage. However, early diagnosis of HCC remains a challenge. Therefore, early diagnosis method using circulating tumor cell (CTC), which is a non-invasive diagnostic method has recently emerged. In this study, by adding graphene oxide to the existing our CTC isolation beads, we investigated whether it could be used in clinical practice by increasing the isolation efficiency of antibody-specific HCC cells.

Methods: Seven HCC male patients who received outpatient and inpatient treatment from May to December 2021 at Chungnam National University were included. Blood samples from these seven patients diagnosed with HCC were collected and clinicopathological information for these patients was investigated in detail through a retrospective review of medical records. And alginate-polyvinyl alcohol (PVA)-graphene (APG) beads were prepared in the sequence of our experiments. This research was approved by the Institutional Review Board of Chungnam National University Hospital (approval no. CNUH 2020-10-088-014).

Results: Testing with APG beads does not require equipment such as centrifugation, and it also has the advantage that it is possible to mass-produce without external pressure. Especially, added graphene oxide enable to increase the separation efficiency of antibody-specific cells by allowing more antibodies to be stably fixed to the bead. This technique allows the rapid and high concentration separation of desired cells in the blood. We analyzed the correlation between CTC count, tumor number, tumor size, HCC stage, serum AFP, and serum PIVKA-II. As shown in the figure below, the CTC counts have a significant correlation with HCC stage and serum PIVKA-II. Although the number of samples was small, it was confirmed that the cancer stage had the greatest correlation with the CTC count among the factors.



Conclusions: By using APG beads in HCC patients, it is expected that it will not only be able to non-invasively diagnose HCC early, but also can be used actively for clinical diagnosis and treatment by predicting the tumor burden.

Keywords: Hepatocellular carcinoma, Stage, Bead, Graphene oxide

PE-261

Macro-Aspartate Aminotransferase in a Patient with Chronic Hepatitis B

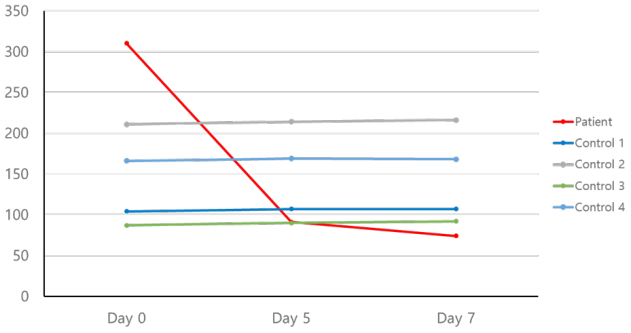
Jae-Hoon Kim[1], Nae-Yun Heo[1], Seungha Park[1], Kyung Ran Jun[2]

[1]Department of Internal Medicine, Inje University College of Medicine, Inje University Haundae Paik Hospital, Busan, Korea, [2]Department of Laboratory Medicine, Inje University College of Medicine, Inje University Haundae Paik Hospital, Busan, Korea

Aims: Although aspartate aminotransferase (AST) is one of serum markers for hepatocellular damage in chronic hepatitis, it is difficult to interpret the case of relatively very high level of AST contrast to normal level of ALT. Macro-AST is a immunoglobulin complex with the enzyme, which may present aberrant high enzymatic activity without significant inflammation in the liver.

Methods: A 50-year-old woman with chronic hepatitis B (CHB) visited the clinic for the evaluation of persistent AST elevation for several years. Initial assessment showed the AST 310 U/L, ALT 17 U/L, CK 79 U/L, HBeAg negative, HBV DNA 3.89x102 IU/mL, normal liver findings in ultrasonography, and transient elastography was 4.9 kPa. Polyethylene glycol (PEG) precipitation test measured the AST activity in the supernatant of mixture of PEG and patient sample, and saline dilution of sample after centrifugation, respectively. Refrigeration storage test measured the AST activity of patient and control samples in time at 4°C at Day 0, Day 5, and Day 7.

Results: In PEG precipitation test, %PEG precipitation activity of AST was 100% in the patient and 68% in control. In refrigeration storage test, the AST activity of the patient was 310 U/L, 91 U/L, and 74 U/L in Day 0, Day 5, and Day 7, respectively. The decrease of AST of patient sample in Day 5 and Day 7 was 70.6% and 76.1%, respectively. In contrast, the levels of AST of controls showed the similar values in time (Figure 1).



Conclusions: The abrupt decrease of AST activity after PEG precipitation, and during refrigeration storage suggests that the relative high value of AST compared with ALT might be contributed to the presence of macro-AST. These non-invasive methods to detect macroenzymes might help the patient avoid unnecessary further work-up.

Keywords: Macroenzyme, Isolated AST elevation, HBV

PE-262

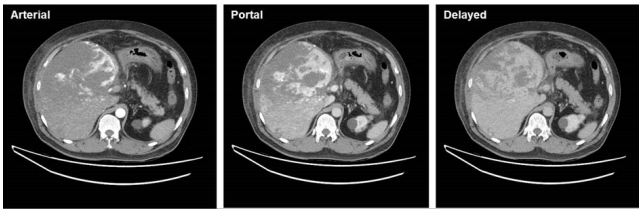
Hepatic Angiosarcoma with Tumor Bleeding Controlled by Embolization

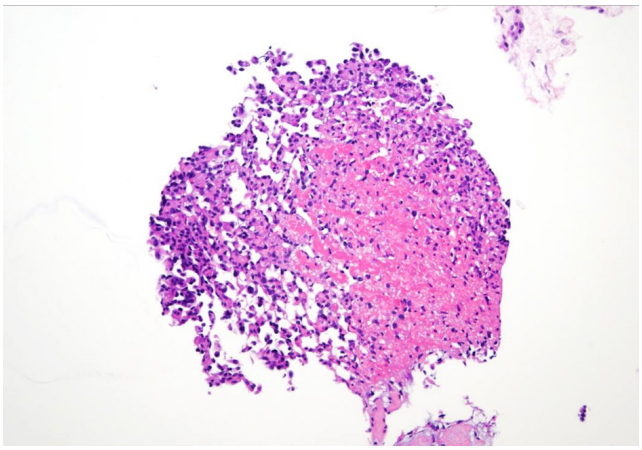
Nae-Yun Heo[1], Kyung Han Nam[2]

[1]Department of Internal Medicine, Inje University Haundae Paik Hospital, Inje University College of Medicine, Busan, Korea, [2]Department of Pathology, Inje University Haundae Paik Hospital, Inje University College of Medicine, Busan, Korea

Aims: Primary hepatic angiosarcoma is a rare but aggressive malignancy and the most common primary malignant mesenchymal tumor of the liver in adults. In case of tumor bleeding, it is difficult to control because it has massive venous blood pooling. However, in some cases, angioembolization may be effective to make hemostasis.

Methods: A 52-year-old man visited the department of emergency medicine complaining of abrupt onset of right flank pain. He had taken a poor oral diet due to early satiety a month before. He presented right subcostal sharp pain and pale conjunctiva. At admission, blood pressure was 110/60 mmHg, pulse rate 97/min, hemoglobin 8.5 g/dL, Platelet count 155,000/mm^3, and PT INR 1.29. He had no history of HBV or HCV infection or alcoholic liver disease. Abdomen CT showed a huge hepatic mass (17×11 cm) in the right anterior segment with low density and multiple nodular enhancing foci with satellite nodules. The main tumor lesion showed contrast extravasation suggestive of active intratumoral bleeding.





Results: Some contrast media leakage was noted on the left hepatic arteriogram, and embolization was performed with gel form slurry. Then, he did not present the progression of anemia. Follow-up liver CT showed disseminated arterial enhancing masses or nodules in both lobes of the liver with a delayed gradual central fill-in enhancement pattern (Fig. 1). A liver biopsy presented irregular anastomosing vascular channels lined by atypical endothelium, which was consistent with angiosarcoma (Fig. 2). On hospital day 12, he expired due to septic shock without chemotherapy.

Conclusions: It is necessary to differentiate primary hepatic angiosarcoma among hypervascular tumors with a bleeding tendency. Although hepatic artery embolization is an option to treat this tumor, it may have a limited role to make hemostasis and lower the risk after liver biopsy.

Keywords: Liver cancer, Angiosarcoma, Embolization

PE-263

The Relationship between Fatty Liver Disease and Thyroid Nodules in Primary Care Institution

Min Seong Kim

Millenium Seoul Internal Medicine Clinic, Incheon, Korea

Aims: Although the relationship between fatty liver disease and thyroid nodules is unknown, fatty liver disease and thyroid cancer are known to be more prevalent. This study is an experimental study investigating the association between thyroid nodules and fatty liver among patients undergoing abdominal and thyroid ultrasonography at a primary care institution.

Methods: Liver function test, thyroid, and abdominal ultrasonography data were performed in parallel for a total of 100 patients at one institution. Thyroid nodules have been classified into five malignant risk categories according to the K - Thyroid Imaging Reporting and Data System (TIRADS). Risk and multivariate analyzes were used to investigate the association between fatty liver and thyroid nodules, including K-TIRADS stratification of thyroid nodules.

Results: Thirty-four (34%) of 100 patients who underwent both thyroid and abdominal ultrasound had fatty liver. The proportion of thyroid nodules in the fatty liver group was higher than in the normal liver group. (50% (17/34) vs 30.3% (19/66), p=0.351). In a multivariate analysis including liver function biochemical tests (AST/ALT/GGT), high-risk nodules (K-TIRADS 4 & 5) tended to be higher in the fatty liver group. (14.7% (5/34) vs 6.1% (4/66), 95% CI 0.5–3.20; p=0.4).

Conclusions: The relationship between fatty liver and thyroid nodules was not statistically significant. Among fatty liver and thyroid nodules, high-risk nodules (K-TIRADS 4.5) appeared to be more associated with fatty liver, but this was not statistically significant. Those more cases would be needed in the future.

Keywords: Fatty liver disease, Thyroid nodule, Thyroid cancer

PE-264

PCKS9 Inhibition Attenuates Steatosis and Inflammation by Ameliorating ER Stress in Non-Alcoholic Fatty Liver Disease Mouse Model

Keum-Jin Yang[1], Seok-Hwan Kim[1,2], Myeong Jun Song[1,2*]

[1]Clinical Research Institute, Daejeon St. Mary`s Hospital, [2]Department of Internal medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Nonalcoholic fatty liver disease (NAFLD) causes significant morbidity and mortality, and pharmacological treatment options are limited. Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the degradation of the low-density lipoprotein receptor (LDL-R) thereby elevating plasma LDL cholesterol levels and the risk of coronary heart disease. Therefore, we investigated the role of PCSK9 inhibitor Evolocumab, a monoclonal antibody in liver fat accumulation and injury for the treatment of NAFLD.

Methods: In this study, we investigated the role of PCSK9 in diet-induced mouse model. Evolocumab (50 mg/kg) or vehicle was administered weekly for 12 weeks to mouse receiving a high fat diet or an iso-

caloric control diet. At the end of the treatment of PCSK9 inhibition, serum and liver samples were obtained for molecular characterization and histopathological analysis.

Results: PCSK9 inhibition with evolocumab reduced high fat-induced hepatic triglyceride accumulation through regulation of lipid metabolism (modulation of the transcription factors (SREBP-1c) in liver and oxidation (PPARα and CPT1)), hepatocellular injury (ALT), hepatic inflammation (pro-inflammatory cytokines/chemokines (IL-1β, IL-6, TNFα, IL-10, and MCP-1). In line with these findings, a metabolic challenge using a high-fat diet attenuates severe hepatic steatosis, ER stress inflammation and fibrosis in the liver of mice treated with evolocumab compared to controls.

Conclusions: We demonstrated that anti-PCSK9 treatment using evolocumab attenuated diet-induced steatohepatitis in the mouse model. Anti-PCSK9 treatment that spares liver metabolism may be a viable new therapeutic possibility for the treatment of NAFLD. Further studies are needed to elucidate the exact role of PCSK9 in NAFLD and to evaluate efficacy and safety of anti-PCSK9 treatment in patients with NAFLD.

Keywords: Nonalcoholic fatty liver disease, Proprotein convertase subtilisin/kexin type 9, ER stress

PE-265

Acute Respiratory Distress Syndrome due to Severe Pneumonitis after Atezolizumab plus Bevacizumab for Hepatocellular Carcinoma Treatment: A Case Report

Su Hyeon Cho[1#], Ga Ram You[2#], Chan Park[3], Sang-Geon Cho[4], Jong Eun Lee[3], Sung Kyu Choi[1], Sung Bum Cho[2], Jae Hyun Yoon[1*]

[1]Department of Gastroenterology and hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea, [2]Department of Gastroenterology and hepatology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea, [3]Department of Radiology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea, [4]Department of Nuclear Medicine, Chonnam National University Hospital and Medical School, Gwanju, South Korea

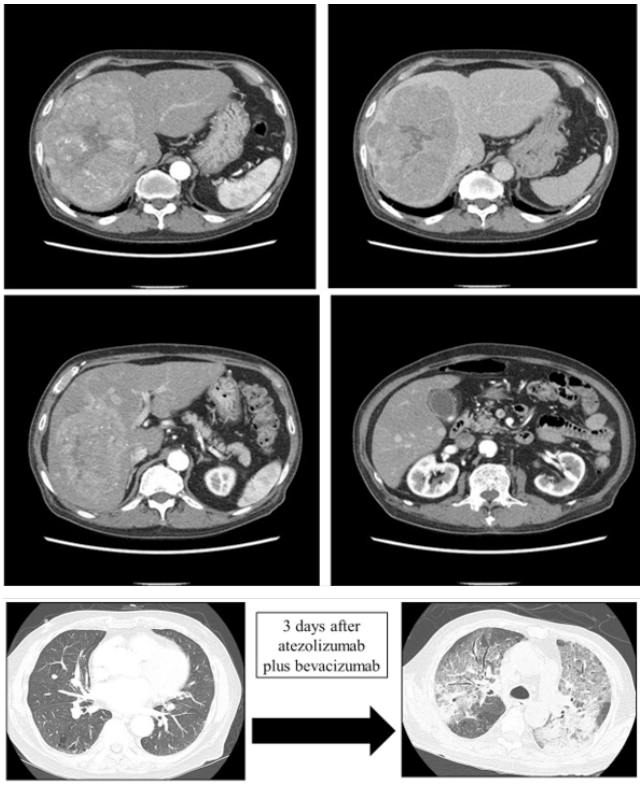
Aims: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and has a high mortality. However, the treatment options for advanced HCC are limited to tyrosine kinase inhibitors, such as sorafenib and lenvatinib. Because of the insufficient treatment efficacy of these previous regimens, the combination therapy of atezolizumab and bevacizumab has been investigated, and the improvement of progression-free and overall survival has been demonstrated. However, the adverse events of this combination therapy in advanced HCC have not been established.

Methods: An 82-year-old male was diagnosed with HCC along with several daughter nodules and extrahepatic metastasis in the bones and lungs. Because of the high burden of the intrahepatic tumor, a transarterial radioembolization (TARE) was performed. Thirty-seven days after the initial TARE, a combination therapy of atezolizumab and bevacizumab was administered. The patient visited the emergency department three days after the combination therapy because of severe dyspnea.

Results: The patient was diagnosed to have severe pneumonitis with acute respiratory distress syndrome based on a computed tomography scan. Despite the prompt management of pneumonitis via administering systemic steroids, lung lesions were not eradicated, and the patient expired 31 hours after admission.

Conclusions: The treatment guidelines for advanced HCC have been recently updated to include the combination of atezolizumab and bevacizumab. Few reports have described the serious adverse events of this combination therapy. Clinicians must be aware of severe pneumonitis due to immune-related adverse events of this combination therapy, and patients should be monitored after therapy.

Keywords: Hepatocellular carcinoma, Systemic therapy, Adverse events, Pneumonitis, Atezolizumab



PE-266

Extrahepatic Recurrence of Hepatocellular Carcinoma after Radiofrequency Ablation or Surgery: Multi-Institutional Study Using Propensity Score Matched Analysis

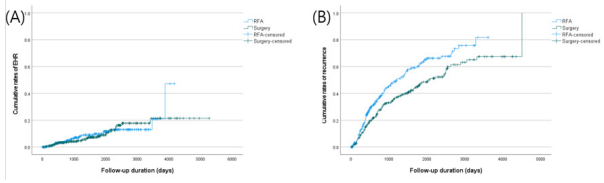
Jae Hyun Yoon[1], Su Hyeon Cho[1], Ga Ram You[1], Sung Bum Cho[2], Yang Seok Ko[3], Chang Hun Lee[4], In Hee Kim[4], Hoon Gil Jo[5], Sung Kyu Choi[1]

[1]Department of Gastroenterology, Chonnam National University Hospital and Medical School, Gwangju, South Korea, [2]Department of Gastroenterology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea, [3]Department of Surgery, Hwasun Chonnam National University Hospital and Medical School, Hwasun, South Korea, [4]Department of Gastroenterology, Chonbuk National University Hospital, Jeonju, Korea, [5]Department of Gastroenterology, Wonkwang University Hospital, Iksan, Korea

Aims: Surgery and radiofrequency ablation (RFA) remains the mainstay of treatment of early stage hepatocellular carcinoma. Although extrahepatic metastasis (EHM) of HCC associated with poor outcomes develops in patients after surgery or RFA, the clinical features and risk factors of EHM of HCC remain unclear. We compared and elucidated the characteristics and risk factors of EHM after surgery of RFA for HCC.

Methods: From January 2008 to December 2019, we retrospectively enrolled 661 patients who underwent RFA and 1069 patients who underwent surgery as first-line treatment for HCC at four tertiary academic hospitals. Using propensity score matching analysis, surgery group patients were 1-on-1 matched to the RFA group using the nearest available pair matching method. Univariate analyses were performed using the chi-squared test, and univariate and multivariate analyses were performed *via* logistic regression, as appropriate.

Results: After propensity score matching analysis, two hundred and ninety-one patients were finally enrolled from each group. There was no difference regarding tumor size and portion of multiple tumors in RFA and surgery group, 2.51±1.20 *vs.* 2.54±1.11 (cm), and 10.6% *vs.* 12.4%, respectively. EHR was diagnosed in 25 patients (8.6%) in RFA group and 28 patients (9.6%) in surgery group (HR 0.93 (0.51-1.60, 95% CI), p=0.803) during a median follow-up period of 1,498 days. The 10-year cumulative rate of EHR were 20.9% in RFA group and 21.5% in surgery group (p=0.803). However, RFA group showed higher recurrence rate of HCC than surgery group (51.9% *vs.* 45.0%, HR 0.67 (0.53-0.85), p=0.001). The 10-year cumulative rate of recurrence of HCC were 81.7% in RFA group and 67.4% in surgery group (p<0.001).



Conclusions: RFA and surgery group showed no difference in EHR in long- term follow-up duration, however RFA group showed higher rates of recurrence rates compared to surgery group.

Keywords: Hepatocellular carcinoma, Extrahepatic recurrence, Radiofrequency ablation, Surgical resection

PE-267

Sarcopenia in Chronic Liver Disease: Easy to Diagnose?

Seong Hee Kang[1], Heechul Nam[2], Eileen L Yoon[3], Sung Eun Kim[4], Ji-Won Park[4], Sang Bong Ahn[5], Dae Won Jun[3]

[1]Department of Internal Medicine, Inje University College of Medicine, [2]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, [3]Department of Internal Medicine, Hanyang University College of Medicine, [4]Department of Internal Medicine, Hallym University Sacred Heart Hospital, [5]Department of Internal Medicine, Eulji University School of Medicine

Aims: A bioelectrical impedance analysis (BIA) which is non-invasive and relatively inexpensive has been a common method in assessing muscle mass. However, controversy remains regarding whether height- or weight-adjusted skeletal muscle mass has a better predictive ability in defining sarcopenia. The objective of this study was to investigate the association between several definitions of sarcopenia based on BIA and liver fibrosis.

Methods: A prospective study was conducted, involving 414 participants who were evaluated with or without sarcopenia using BIA. The skeletal muscle index (SMI) was calculated as the appendicular skeletal muscle mass divided by height, total body mass (kg) and body mass index (BMI). The degree of liver fibrosis was assessed by APRI, FIB-4 and transient elastography (TE). Steatosis was assessed by ultrasound and CAP score. Participants with both low muscle mass and hand grip strength were diagnosed with sarcopenia.

Results: Consecutive 414 patients with liver disease were included in the study (197 [47.5%] male, mean age 53.5). 236 (57.0%) patients were nonalcoholic fatty liver disease, 144 (34.8%) viral hepatitis and 25 (6.0%) alcohol hepatitis. While both height-adjusted SMI (r=-0.235; p<0.001) and hand grip strength (r=-0.323; p<0.001) showed an inverse correlation with the FIB-4 score, weight-adjusted SMI (r=-0.181; p=0.002) showed an inverse relationship with liver stiffness by TE. In sub-analysis according to sex, there was a similar correlation between SMI and fibrosis marker. Regarding steatosis, weight-adjusted SMI (r=-0.180; p=0.002) showed an inverse relationship with CAP score, but height/BMI-adjusted SMI and hand grip strength showed a positive correlation.

Conclusions: Liver fibrosis is associated with sarcopenia when using height/weight-adjusted SMI. However, the relationship between SMI and steatosis showed contradictory results. Our findings have potential clinical significance because the different operational methods used to calculate SMI by BIA could substantially influence study results.

Keywords: Sarcopenia, Chronic liver disease, Bioelectrical impedance analysis, Liver fibrosis

PE-268

Comparison of Magnetic Resonance Elastography and Transient Elastography to Detect Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease: A Systemic Review and Meta-Analysis

Seong Hee Kang[1], Jeong-Ju Yoo[2], Yuri Cho[3], Hye-Won Lee[4], Do Seon Song[5], Sang Bong Ahn[6], Miyoung Choi[7] Dae Won Jun[8]

[1]Department of Internal Medicine, Inje University College of Medicine, Korea, [2]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Korea, [3]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Korea, [4]Department of Internal Medicine, Yonsei University College of medicine, Korea, [5]Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, [6]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University College of Medicine, Korea, [7]Clinical Evidence Research, National Evidence-based Healthcare Collaborating Agency, [8]Department of Internal Medicine, Hanyang University College of Medicine, Korea

Aims: Non-alcoholic fatty liver disease (NAFLD)-related advanced hepatic fibrosis is associated with liver and cardiovascular morbidity and mortality. Magnetic resonance elastography (MRE) and transient elastography (TE) are well-established methods for liver fibrosis staging. We conducted a systemic review and meta-analysis to compare the diagnostic performance of MRE vs TE for staging of liver fibrosis

in patients with NAFLD.

Methods: PubMED/MEDLINE, EMBASE and the Cochrane Library were searched for studies examining the diagnostic accuracy of these index tests, against histology as the reference standard, in adult patients with NAFLD from January 2008 to July 2020. Two authors independently screened and assessed methodological quality of studies and extracted data. Summary estimates of sensitivity, specificity, and area under the curve (sAUC) were calculated for detecting advanced fibrosis and cirrhosis.

Results: We included 25 studies (7,054 patients) with 17 TE and 10 MRE for diagnosing fibrosis stages. sAUC for diagnosis of advanced fibrosis were: 0.83 for TE and 0.93 for MRE. sAUC for diagnosis of cirrhosis were: 0.95 for TE and 0.91 for MRE. TE had summary sensitivity and specificity values of 90.0% and 72.0% at cutoff values of 7.6-7.9 kpa for advanced fibrosis and 79% and 90% at cutoff values of 11.5-11.95 kpa for cirrhosis. MRE had summary sensitivity and specificity values of 89.0% and 93.0% at cutoff values of 3.4-3.64 kpa for advanced fibrosis and 96.0% and 97.0% at cutoff values of 5.1-6.7 kpa for cirrhosis.

Conclusions: In a meta-analysis of data from individual participants with biopsy-proven NAFLD, TE and MRE have acceptable diagnostic accuracy for advanced fibrosis and cirrhosis.

Keywords: NAFLD, MRE, Transient elastography, Liver fibrosis

PE-269

The Significance of Radical Resection in T2 GB Cancer

Yunkyung Woo[1], Dongdo You[*1], Taeho Hong[2], Jaehyun Han[1], Hojung Choi[2], Kwangyeol Paik[3]

[1]Surgery, The Catholic University of Korea St. Vincent's Hospital, Republic of Korea, [2]Surgery, The Catholic University of Korea Seoul St. Mary's Hospital, Republic of Korea, [3]Surgery, The Catholic University of Korea Yeouido St. Mary's Hospita, Republic of Korea

Aims: AJCC 8th Edition has proposed tumor location of GB cancer is included in T2 stage.

Methods: Between 2010 to 2019, a consecutive series of 118 patients with pathologic T2 gallbladder carcinoma that underwent surgery at Seoul St. Mary Hospital and St. Vincent Hospital were retrospectively analyzed. Review of pathologic slides and preoperative image for tumor location were performed. Wedge or IVb/V of hepatic resection and harvested lymph node ≥3 lymph node are the definition of radical resection.

Results: The accuracy of preoperative tumor location was 75 of 110 (68%) patients. Univariate analysis shown that increased CA19-9, tumor differentiation, perineural invasion, N stage were associated with overall survival and increased CA 19-9, perineural invasion and radical resection still remained to be prognostic factor in multivariate analysis.

Conclusions: The surgical approach based on preoperative tumor location might be hazardous. Extended cholecystectomy includes hepatic resection and harvested lymph node ≥3 lymph node could improve overall survival

Keywords: GB cancer, Radical resection, Tumor location

PE-270

Metabolic Dysfunction-Associated Fatty Liver Disease Criteria Better Identify Subjects with High-Risk Fatty Liver Disease: A Nationwide Study

Ho Soo Chun[1], Eugene Han[2], Yong-ho Lee[3,4], Jae Seung Lee[3,5], Hye Won Lee[3,5], Beom Kyung Kim[3,5], Jun Yong Park[3,5], Do Young Kim[3,5], Sang Hoon Ahn[3,5], Byung-Wan Lee[3,4], Eun Seok Kang[3,4], Bong-Soo Cha[3,4], Seung Up Kim[3,5]

[1]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [4]Institute of Endocrine Research, Yonsei University College of Medicine, Seoul, Korea; 5Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: Clinical features of nonalcoholic fatty liver disease (NAFLD) that should constitute the diagnostic criteria of metabolic dysfunction-associated fatty liver disease (MAFLD) remain unclear. We investigated the risk of sarcopenia and cardiovascular disease (CVD) in MAFLD and non-metabolic risk (MR) NAFLD.

Methods: Subjects were selected from the Korean National Health and Nutrition Examination Surveys 2008–2011. Significant liver fibrosis was defined based on the fibrosis-4 index, categorized by age cut-offs. Sarcopenia was defined as the lowest quintile sarcopenia index. An atherosclerotic CVD (ASCVD) risk score >10% was defined as high probability.

Results: Of the 7,248 subjects with fatty liver, 7,111 (98.1%) had MAFLD and 137 (1.9%) had non-MR NAFLD. In the non-MR NAFLD group, 28 (20.4%) had significant fibrosis. MR components were statistically similar between subjects with and without significant fibrosis in the non-MR NAFLD group (P>0.05), but were significantly higher in the MAFLD group than in the non-MR NAFLD group (p<0.05). After adjusting for confounders, the risks of sarcopenia and high ASCVD probability were similar between subjects with and without significant fibrosis in the non-MR NAFLD group (all P>0.05); the risks were significantly higher in the MAFLD group than in the non-MR NAFLD group (odds ratio=3.38-7.23 for sarcopenia and 3.73-6.64 for ASCVD; all p<0.05).

Table. Adjusted risks of sarcopenia or high probability of ASCVD in MAFLD and non-MR NAFLD stratified according to fibrotic burden.

	Non-MR NAFLD		
Sarcopenia	Without significant liver fibrosis	With significant liver fibrosis	MAFLD
Model 1	1.00 (ref.)	3.84 (0.85-17.20) P=0.079	7.23 (2.67-20.63) P<0.001
Model 2	1.00 (ref.)	4.20 (0.90-19.67) P=0.069	3.56 (1.25-10.12) P=0.018
Model 3	1.00 (ref.)	4.51 (0.97-21.04) P=0.055	3.38 (1.18-9.65) P=0.023
ASCVD			
Model 1	1.00 (ref.)	1.52 (0.34-6.78) P=0.581	6.64 (2.87-15.36) P<0.001
Model 2	1.00 (ref.)	1.59 (0.36-6.98) P=0.539	5.47 (2.39-12.73) P<0.001
Model 3	1.00 (ref.)	3.01 (0.60-15.13) P=0.180	3.73 (1.52-9.13) P=0.004

Model 1: adjusted for sex and age.
Model 2: adjusted for sex, age, body mass index, and waist circumference.
Model 3: adjusted for sex, age, body mass index, waist circumference, HOMA-IR*, HDL-cholesterol*, triglycerides*, systolic blood pressure, fasting blood glucose, aspartate aminotransferase*, alanine aminotransferase*, gamma glutamyltransferase*, and fatty burden by fatty liver index.
*Log-transformed.

Conclusions: The risk of sarcopenia and CVD were significantly higher in the MAFLD group but did not differ according to fibrotic burden in the non-MR NAFLD group. The MAFLD criteria might be better for identifying high-risk fatty liver disease than the NAFLD criteria.

Keywords: Metabolic dysfunction-associated fatty liver disease, Non-alcoholic fatty liver disease, Sarcopenia, Cardiovascular disease

PE-271

Risk Stratification according to Sarcopenic and Metabolic Status among Overweight/Obese Subjects with Metabolic Dysfunction-Associated Fatty Liver Disease

Ho Soo Chun[1,2], Minjong Lee[1,2], Han Ah Lee[1,2], Hwi Young Kim[1,2], Tae Hun Kim[1,2], Sang Hoon Ahn[3,4], Seung Up Kim[3,4]

[1]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Ewha Womans University Medical Center, Seoul, Korea; [3]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [4]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Aims: Sarcopenia is a significant indicator of the severity of nonalcoholic fatty liver disease (NAFLD). We investigated whether sarcopenia and metabolic status could identify subgroups with different risk of liver fibrosis and atherosclerotic cardiovascular disease (ASCVD) among overweight and obese subjects with metabolic dysfunction-associated fatty liver disease (MAFLD).

Methods: This multicenter, retrospective study involved 16,564 overweight and obese MAFLD subjects without diabetes who underwent a health screening program (2014–2020). Sarcopenia was defined based on gender-specific sarcopenia index (SI) cutoff using multi-frequency bioelectric impedance analysis. The metabolic unhealthy (MU) status was defined as 2 or more metabolic risk abnormalities. Significant liver fibrosis was defined as fibrosis-4 (FIB-4) index >2.67, or NAFLD fibrosis score (NFS) >0.676. High probability of ASCVD was defined as ASCVD risk score >10%.

Results: The prevalence of MU-MAFLD was 75.7% (n=12,504 of 16,564), and the proportion of sarcopenic subjects was 7.5% (n=936) among those with MU-MAFLD. After adjusting for confounders, the risk of significant liver fibrosis significantly increased from non-sarcopenic subjects with MU-MAFLD (odds ratio [OR]=3.47 by FIB-4 and 7.31 by NFS) to sarcopenic subjects with MU-MAFLD (OR=7.95 by FIB-4 and 23.58 by NFS), compared with metabolic healthy (MH) subjects with MAFLD (all p<0.001). The risk for high probability of ASCVD significantly increased from non-sarcopenic subjects with MU-MAFLD (OR=1.72) to sarcopenic subjects with MU-MAFLD (OR=3.99), compared with subjects with MH-MAFLD (all p<0.001).

Conclusions: The risks of significant liver fibrosis and ASCVD differed significantly according to sarcopenic and metabolic status among overweight and obese subjects with MAFLD.

Keywords: Metabolic dysfunction-associated fatty liver disease, Sarcopenia, Liver fibrosis, Atherosclerotic cardiovascular disease

Table. Adjusted risk of significant liver fibrosis and high probability of ASCVD according to the status of sarcopenia.

	Model 1			Model 2			Model 3		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Significant liver fibrosis by FIB-4									
MH-MAFLD		1 (reference)			1 (reference)			1 (reference)	
MU-MAFLD without sarcopenia	3.05	2.10-4.42	<0.001	3.41	2.23-5.22	<0.001	3.47	2.27-5.31	<0.001
MU-MAFLD with sarcopenia	8.43	5.52-12.86	<0.001	8.40	5.15-13.71	<0.001	7.95	4.86-13.01	<0.001
Significant liver fibrosis by NFS									
MH-MAFLD		1 (reference)			1 (reference)			1 (reference)	
MU-MAFLD without sarcopenia	6.07	3.55-10.40	<0.001	7.26	4.15-12.69	<0.001	7.31	4.18-12.78	<0.001
MU-MAFLD with sarcopenia	20.70	11.69-36.66	<0.001	24.94	13.65-45.58	<0.001	23.58	12.89-43.12	<0.001
High probability of ASCVD									
MH-MAFLD		1 (reference)			1 (reference)			1 (reference)	
MU-MAFLD without sarcopenia	2.47	2.13-2.87	<0.001	1.70	1.45-2.00	<0.001	1.72	1.46-2.02	<0.001
MU-MAFLD with sarcopenia	6.05	4.90-7.46	<0.001	3.90	3.12-4.87	<0.001	3.99	3.18-5.01	<0.001

Model 1 = Age*, gender.
Model 2 = Model 1 + hypertension, dyslipidemia, AST, ALT, and creatinine.
Model 3 = Model 2 + alcohol, smoking, malignancy, and medication.
aOR, adjusted odds ratio; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; FIB-4, fibrosis-4 index; MAFLD, metabolic dysfunction associated fatty liver disease; MH, Metabolic healthy; MU, Metabolic unhealthy; NFS, NAFLD fibrosis score.
*Age was applied as a categorical variable with a median cut-off value of 48.

PE-272

The Density of Portal T-Cell Infiltration Effects Clinical Outcomes in Chronic Hepatitis GVHD after Allogenic Stem Cell Transplantation: A Comparison to Autoimmune Liver Diseases

Soon Kyu Lee[1,2], Pil Soo Sung[1,2*], Jihoon Kim[1,2], Ji Won Han[1,2], Si Hyun Bae[1,2], Jung Hyun Kwon[1,2], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2]

[1]Division of gastroenterology and hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [2]The Catholic University Liver Research Centre, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [3]Division of gastroenterology and hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea, [4]Division of gastroenterology and hepatology, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

Aims: Graft-versus-host disease (GVHD) is a major cause of morbidity and mortality in patients who undergo allogeneic hematopoietic stem cell transplantation. In this study, we investigated the impact of histological characteristics of chronic hepatic GVHD on clinical outcomes.

Methods: Thirty-eight patients with biopsy-confirmed chronic hepatic GVHD between May 2016 and June 2021 were enrolled. Moreover, forty patients with biopsy-confirmed autoimmune liver diseases were also enrolled. Immunohistochemical staining for CD3, CD68, CD38, CD20, and CK19 was performed to identified immune cell types infiltrated in the liver. Cholestatic variant was defined as the R-value <2.0, which was calculated by alanine aminotransferase (ALT) divided by alkaline phosphatase (ALP). The primary outcome was biochemical response at 4 weeks (early) and 8-12 weeks (late) after corticosteroid treatment. The secondary outcomes were the overall survival (OS) and liver-related event-free survival (EFS). Liver-related event were defined as liver failure or liver transplantation (LT).

Results: Among 38 included hepatic GVHD patients, the cholestatic variant (n=19) showed higher level of bilirubin than hepatitic variant (n=19). In the hepatitic group, periportal areas demonstrated prominent inflammation with a main population of T cells. In the cholestatic group, ductulitis and ductopenia was predominantly identified. The hepatitic group demonstrated significantly higher early (p=0.015) and late (p=0.05) than the cholestatic group. The rate

of relapse after treatment response was marginally lower in hepatitic group. Moreover, the hepatitic group showed significantly better OS (p=0.026) and liver-related event EFS (p=0.036) than the cholestatic group. There was no liver-related event in the hepatitic group, whereas three patients in the cholestatic group died from liver-related event. Meanwhile, autoimmune hepatitis group (AIH, n=29) demonstrated severe infiltration of CD3+ cells in periportal area than primary biliary cholangitis group (PBC, n=19). The density of infiltrated CD3+ cells in periportal area were significantly higher in hepatitic and AIH groups, followed by PBC and cholestatic groups. AIH group demonstrated higher treatment response compared to PBC group. However, both groups showed higher rate of treatment response compared to hepatitic group.

Conclusions: n our study, hepatitic variants with portal T cell infiltration shows better outcomes than cholestatic variants in patients with chronic hepatic GVHD.

Keywords: Gvhd, Autoimmune hepatitis, Primary biliary cholangitis, T cell

PE-273

The Effect of Fecal Material Transplantation on Hepatic and Brain Diseases in a Non-Human Primate Model: Several Considerations for Future Application to Liver Disease Patients

Seok-Hwan Kim[*1], Bon-Sang Koo[2], In-Sang Song[1], Gwang-Sik Chun[1], Sun-Jong Han[1]

[1]Surgery, Chungnam National University, Republic of Korea, [2]National Primate Center, Korea Research Institution Of Bioscience And Biotechnology, Republic of Korea

Aims: Recently, fecal microbiome transplantation (FMT) has been used to show effective treatment for human diseases. A preclinical animal model, a primate animal model most similar to humans, to study the overall physical effects of intestinal microflora and probiotics, and the direct effects on the liver and brain, is a very challenging and innovative task that is attempted for the first time in the world.

Methods: Acquisition of primates (9 animals) (Cynomolgus monkeys). Feces obtained from chronic diarrheal disease monkeys were transplanted into primates' transverse colons using FMT. Oral administration of human-derived probiotic strains to primates for six weeks (3 times). A sampling of liver tissue and portal vein blood through surgical treatment of primates. Microbiome analysis by performing 16S rRNA sequencing on fecal samples 2 and 6 weeks after fecal microbial transplantation and probiotics administration. Performing blood sampling from primates' femoral vein and hepatic portal vein. Hematological/blood biochemical analysis on obtained blood samples. Confirmation of inflammation induction through radiological analysis (18FDG PET-CT) analysis of primates. Metabolome analysis, such as fatty acids in the blood and hormones in the CSF.

Results: In blood samples from the portal vein, severe neutropenia was consistently observed in the subjects of fecal microbial transplant. The probiotics administration group observed no significant change in neutrophils. However, in the case of lymphocytes, a decrease or increase was observed for each individual. As a result of analysis before/after primate fecal microbial transplantation, a statistically significant increase in insulin, C-peptide, MCP-1, ACTH, and GH levels was observed. No changes in hormone levels were observed according to the fecal condition (diarrhea, normal stool) of fecal microbial transplantation. As a result of analysis before/after the administration of primate probiotics per oral, no significant changes in hormone levels were observed.

Conclusions: A significant change in the neutrophil/lymphocyte ratio in the portal vein is one of the considerations for the effect of FMT on the treatment of hepatocellular carcinoma. Hormonal changes in CSF may help control metabolic diseases (diabetes, hyperlipidemia) following immunosuppressive drugs in liver transplant patients. Considering that oral probiotics intake and the effect of FMT on primates are different, it will be necessary to view the route of administration when developing microbiome therapeutics in the future.

Keywords: Non-human primate, Fecal material transplantation, Liver disease

PE-274

Ultrasound-Based Deep Learning Model for Detection and Classification of Focal Liver Lesions

Seung Kak Shin[1], Young Jae Kim[2], Kwang Gi Kim[2], Oh Sang Kwon[1], Ju Hyun Kim[1], Yun Soo Kim[1*]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea, [2]Department of Biomedical Engineering, Gachon University College of Medicine, Incheon, Republic of Korea

Aims: Abdominal ultrasound is an imaging modality of choice for screening and surveillance of hepatocellular carcinoma (HCC). Experience of ultrasound operators is a factor affecting the sensitivity in detecting focal liver lesions (FLLs) during ultrasound examination. Recently, it has been suggested that the application of artificial intelligence could help to assist physicians in radiologic imaging diagnosis and to reduce individual differences. We aimed to evaluate the usefulness of deep learning-based on liver ultrasound for detection and classification of FLLs including HCC, hepatic hemangioma and cyst.

Methods: Our proposed deep learning model was based on B-mode ultrasound images of 1383 HCCs confirmed by pathology or computed tomography/magnetic resonance imaging, 1067 hepatic hemangiomas, and 966 hepatic cysts, which was stratified by 5-fold cross-validation method. The DeeplabV3 network was used for the deep learning model for FLLs segmentation and the EfficientNet-B2 was used for the deep learning model for classification. The performances including precision, recall rate, F1-score and area under the curve (AUC) were evaluated.

Results: In our model, the detection rate for FLLs was 89.1% when the threshold of intersection over union was set to 0.2. In addition, the classification performances for HCCs were 75.4% of recall, 80.5% of precision, 77.9% of F1-score, and 0.854 of AUC, respectively. The classification performances for hepatic hemangiomas were 67.4% of recall, 63.2% of precision, 64.8% of F1-score, and 0.836 of AUC, respectively. The classification performances for hepatic cysts were 91.2% of recall, 86.2% of precision, 88.6% of F1-score, and 0.989 of AUC, respectively.

Conclusions: We developed an ultrasound-based deep learning mod-

el for detection and classification of focal liver lesions. This model may help minimize the difference of operator-dependent detection rate in ultrasound for surveillance of HCC.

Keywords: Artificial intelligence, Focal liver lesions, Deep learning, Hepatocellular carcinoma, Surveillance

PE-275

Clinical and Molecular Characteristics of Pathologic Subtype in Cholangiocarcinoma

Keun Soo Ahn, Tae-Seok Kim, Yong Hoon Kim, Koo Jeong Kang

Surgery, Keimyung University Dongsan Hospital, Republic of Korea

Aims: Pathologically, cholangiocarcinoma (CCA) can be divided as two pathological subtype; large duct type and small duct type. It represents different origin and carcinogenesis of CCA. However, its clinical impact and molecular characteristics are not well known yet, and we evaluated clinical and molecular features according to pathological subtype.

Methods: On 3 different cohort (Korea ; Keimyung University Dongsan Hospital, USA ; Mayo clinic, TCGA), 107 cases of CCA were included which had available clinical and molecular data (RNA sequencing with mutation). For Korea and USA data, we performed next generation RNA sequencing and RNA expression, variants and fusions were analyzed. For TCGA data, we downloaded clinical and genetic information from TCGA serve. We analyzed clinical and molecular features for them.

Results: On large duct type, frequency of extrahepatic CCA (Klatskin and distal bile duct ca), periductal infiltrating type, history of cholangitis or IHD stone, and N1 stage were significantly high compared to small duct type. In addition, level of serum CEA and CA 19-9 were significantly high in large duct type. In small duct type, history of hepatitis was significantly frequent than large duct type. In both type, frequency of mass forming type was similar. Patients with large duct type showed significant poor disease-free and overall survival than those with small duct type. On multivariate analysis, large duct type, lymph node metastasis and vascular invasion were independent poor prognostic factors. On mutation analysis, KRAS, PIK3CA gene mutation was common in large duct type, whether IDH1/2 mutation and FGFR2 fusion were common in small duct type. On pathway analysis, inflammation related, AKT, Wnt and KRAS related signalling were enriched in large duct type, while metabolism and EMT related pathways were enriched in small duct type.

Conclusions: Two pathological subtypes of intrahepatic CCA with distinct clinical, biological and prognostic differences were identified. Therefore, molecular characteristic of CCA can be predicted based on pathological subtype, and it may lead to more rational targeted approaches to treatment.

Keywords: Cholangiocarcinoma, Pathology, Molecular

PE-276

Autoimmune Hepatitis after Anti-SARS-CoV-2 Vaccination: Systematic Review and Meta-Analysis

Hye Won Lee[1], Won Ki Woo[2], Jae Il Shin[3], Seung Up Kim[1]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Department of thoracic surgery, Yonsei University College of Medicine, Seoul Korea; [3]Department of pediatrics, Yonsei University College of Medicine, Seoul, Korea

Aims: Vaccination against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is associated with autoimmune hepatitis. A systematic review and meta-analysis were conducted to assess the incidence of acute liver failure (ALF) following after SARS-CoV-2 vaccination.

Methods: Patients diagnosed with autoimmune hepatitis following administration of the anti-SARS-CoV-2 vaccine from Pfizer, Moderna or AstraZeneca were eligible. ALF was diagnosed when the prothrombin time international normalized ratio exceeded 1.5 or total bilirubin level exceeded 11.7 mg/dL.

Results: Of the 49 study participants, the majority were females (n=34, 69.4%), and the median age was 62 years. Forty (81.6%) patients received mRNA vaccines, and 17 (34.7%) developed ALF. The rate of ALF was significantly lower among patients who received mRNA vaccines (28.6% vs. 77.8%, p=0.001). Among the 12 patients who underwent liver biopsy, lobular hepatitis was identified in 12 (100%), eosinophilic infiltration in 6 (50%), and cholestasis and bile duct injuries in 2 (16.7%). Additionally, 4 (33.3%) patients in the non-ALF group had histologic fibrosis. Forty-two patients were treated with steroids with and without azathioprine; one underwent plasma exchange. Administration of Vaccines other than the mRNA vaccine (odds ratio [OR]=15.7, 95% confidence interval [CI]=1.32–188.0, p=0.029) and an aspartate transaminase level > 1,000 IU/L (OR=17.2, 95% CI=1.6–185.0, p=0.019) were independent predictors of ALF. Five patients died due to autoimmune hepatitis after anti-SARS-CoV-2 vaccination.

Conclusions: SARS-CoV-2 vaccination can cause acute live injury. Thus, patients who experience liver-related symptoms or liver enzyme abnormalities should be monitored closely.

Keywords: Autoimmune hepatitis, SARS-CoV-2 vaccination, Acute liver failure

PE-277

Real-World Efficacy and Safety of Cabozantinib in Korean Patients with Advanced Hepatocellular Carcinoma: A Multicenter Retrospective Analysis

Yeong Hak Bang[1*], Choong-kun Lee[2*], Changhoon Yoo[1†], Hong Jae Chon[3], Moonki Hong[2], Beodeul Kang[3], Hyung-Don Kim[1], Sook Ryun Park[1], Won-Mook Choi[4], Jonggi Choi[4], Danbi Lee[4], Ju Hyun Shim[4], Kang Mo Kim[4], Young-Suk Lim[4], Han Chu Lee[4], Min-Hee Ryu[1], Baek-Yeol Ryoo[1†]

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, [2]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea, [3]Medical Oncology, Department of Internal Medicine, CHA Bundang Medical Center,

CHA University, Seongnam, Korea, [4]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Aims: Cabozantinib, a multiple kinase inhibitor, was recently approved for patients with previously treated unresectable hepatocellular carcinoma (uHCC). We aimed to investigate the safety and efficacy profiles of cabozantinib.

Methods: This multicenter retrospective study included 110 patients with uHCC who received cabozantinib after progression on other systemic treatments between October 2019 and May 2021.

Results: The median age was 58 years (range, 20-77), and 98 (89.1%) were male. Prior to cabozantinib, all patients were treated with other systemic therapies: sorafenib (n=104, 94.5%) and regorafenib (n=91, 82.7%) were the most commonly used agents. Immune checkpoint inhibitors were previously used in 93 patients (84.5%). Cabozantinib was used beyond the 3rd line of therapy in most patients (n=90, 81.8%). With a median follow-up duration of 11.9 months (95% confidence interval [CI], 10.8-17.2), the median progression-free survival (PFS) was 3.7 months (95% CI, 3.1 and 4.9), and the median overall survival (OS) was 7.5 months (95% CI, 5.5 and 9.5). The disease control rate and overall response rate were 66.3% and 3.6%, respectively. In Child-Pugh A cohort (n=88), the ORR was 4.5%, and the median PFS and OS were 4.3 months (95% CI, 3.6-5.8) and 9.0 months (95% CI, 7.5-11.7), respectively.

Conclusions: Cabozantinib showed consistent efficacy outcomes with prior phase III trial, although this was used as later-line therapy for patients who were refractory to multiple systemic treatments, including immune checkpoint inhibitors.

Keywords: Hepatocellular carcinoma, Cabozantinib

PE-278

Gene Regulatory Network Analysis on snRNAseq Revealed Key Regulators for Hepatocellular Carcinoma Progression

Jeayeon Park[2], Taehong Min[1*], Min Kyung Park[2*], Jeongin Lee[1], Minsoo Choi[3], Su Jong Yu[2@], Junil Kim[1@]

[1]School of Systems Biomedical Science, Soongsil University, Seoul, [2]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, [3]NetTargets Inc., BIO Venture Center, KRIBB, Daejeon, Republic of Korea

Aims: Hepatocellular carcinoma (HCC) is the sixth most common cancer with a high rate of mortality, particularly in the advanced stages. While targeted therapy and immunotherapy have been developed to treat HCC, the response rate for these therapies remains low. Therefore, there is a pressing need to uncover the underlying molecular mechanisms of HCC development.

Methods: We performed single nucleus RNA sequencing (snRNAseq) on biopsy samples collected from six HCC patients with different stages according to the Barcelona Clinic Liver Cancer (BCLC) system. To identify the key regulators of cancer cell heterogeneity, we applied TENET, a gene regulatory network (GRN) inference tool that uses pseudotime-ordered single cell expression data.

Results: Our analysis revealed that the gene expression patterns of carcinoma cells were highly heterogeneous and primarily dictated by BCLC stage (Figure 1). Through the TENET analysis, we were able to identify several key regulatory factors that were previously known to play critical roles in HCC progression. Furthermore, we also identified new potential therapeutic targets for HCC.

Conclusions: This study suggests that GRN analysis with single cell data may provide valuable insights into the molecular mechanisms of HCC development and identify potential therapeutic targets for advanced HCC.

Keywords: Hepatocellular carcinoma, Single nucleus RNA sequencing, Barcelona clinic liver cancer

PE-279

Rare Recurrence of Hepatic Encephalopathy Associated with Embolization of Extrahepatic Portosystemic Shunt in Patients with Recurrent of Hepatic Encephalopathy

JW Park[1], JS Kim[1], Yook Kim[2], HB Chae[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine and Medical Research Institute, Cheongju, Korea, [2]Department of Radiology, Chungbuk National University Hospital, Chungbuk National University College of Medicine and Medical Research Institute, Cheongju, Korea

Aims: Hepatic encephalopathy(HE) occurs above 10% in liver cirrhosis patients. This complication can be considered as natural course or the major complication of cirrhosis itself, but extrahepatic portosystemic shunt (EHPSS) can be another aggravating factor of encephalopathy. Recently several researchers reported that EHPSS affected the recurrence of encephalopathy and also the mortality. So, the early diagnosis and treatment of EHPSS is important to improve the prognosis. We want to assess the effectiveness of EHPSS embolization for the treatment of recurrent HE in patients with cirrhosis.

Methods: The retrospective cohort studies compared the treatment group (7 patients) who had extrahepatic portosystemic shunt with embolization with control group patients (9patients) in liver cirrhosis patients with recurrent hepatic encephalopathy. The patient was collected in single center from Jan 2012 to Aug 2022.

Results: Baseline charactersistics were similar in the two groups. Both the 1 year HE recurrence rate and mortality were not significantly lower in the treatment group than in the control group, whereas there were lower tendency in the treatment group. Only one patient out of seven had recurrence of HE in 3 month, but 4 patients in the control group had recurrence of HE; two in one month, one in 7 month, one in 8 month. Their one year survival rate was similar 53.6% vs 44.4% (p=0.655). Their 1 year HE recurrence tended to be different 14.3% vs. 44.4% (p=0.236). Both MELD and CTP score had the highest HR for mortality even though it is statistically insignificant.

Conclusions: Embolization reduced the recurrence of HE in liver cirrhosis patient with EHPSS. But the number is too small to prove it. We suggest that at the initial stage of patient encounter, to try to search EHPSS and embolize this shunt can prevent the recurrence of HE, and improve the mortality.

Keywords: Liver cirrhosis, Hepatic encephalopathy, Extrahepatic

portosystemic shunt, Embolization

Table 1. Baseline Charactersitics of the Study

	Embolization	Control	P value
No	7	9	
Age, years	61(45-72)	57(53-60.5)	0.95
Male gender(%)	29	67	0.955
Etiology			
HBV	0	1	0.16
Alcohol(%)	4(57)	8(89)	
others	3	0	
No. of HE episodes during the previous 12 months			
1~2	5	6	0.294
≥3	2	0	
HE grade, maximum			
Ⅱ	3	4	0.824
Ⅲ~Ⅳ	2	3	
Portosystemic shunt			
Splenorenal	6		
Mesocaval	1		
Esophageal varix(%)	4(57)	6(67)	0.935
Albumin (g/dL)	3.1(2.8-3.4)	3.0(2.4-3.05)	0.456
Bilirubin (mg/dL)	2.23(1.38-2.44)	1.82(0.67-5.56)	0.288
Creatinine (mg/dL)	0.78(0.48-0.86)	0.87(0.79-1.48)	0.203
INR	1.30(1.27-1.67)	1.37(1.14-1.87)	0.716
MELD	8.32(5.59-14.71)	10.53(7.88-20.73)	0.256
CTP score	9(7-9)	9(7.5-11.5)	0.567

HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; INR, international normaized ratio; MELD, model for end-stage liver disease; CTP, Chil-Turcotte-Pugh

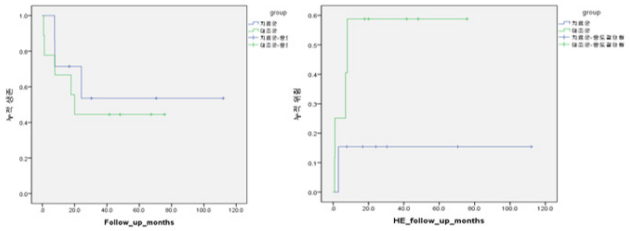


Figure 1 Kaplan-Meier analysis of patient overall survival (a) and recurrence of hepatic encephalopahty (b) in the embolization and control groups.

PE-280

Diagnostic Performance of Fibrosis-4 Index and NAFLD Fibrosis Score in at-Risk Group from Low Prevalence Population

Huiyul Park[1§], Eileen L. Yoon[2,3§], Mimi Kim[4], Jonghyun Lee[5], Hye-Lin Kim[6], Seon Cho[7], Eun-Hee Nah[7*], Dae Won Jun[2,3,5*]

[1]Department of Family Medicine, Myoungji Hospital, Hanyang University College of Medicine, Seoul, Korea, [2]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea, [3]Hanyang Institute of Bioscience and Biotechnology, Hanyang University, Seoul, South Korea, [4]Department of Radiology, Hanyang University College of Medicine, Seoul, Korea, [5]Department of Translational Medicine, Hanyang University Graduate School of Biomedical Science and Engineering, Seoul, Korea, [6]College of Pharmacy, Sahmyook University, Seoul, Republic of Korea, [7]Department of Laboratory Medicine, Health Promotion Research Institute, Seoul, Korea

Aims: Most guidelines recommend screening for advanced hepatic fibrosis using fibrosis-4 index (FIB-4) not only in non-alcoholic fatty liver disease (NAFLD) subjects but also in the so-called 'at risk group'. However, there has been no study on the diagnostic performance of FIB-4 in 'at risk groups' other than NAFLD and diabetes. We aimed to evaluate the diagnostic performance of FIB-4 in 'at-risk group' with advanced hepatic fibrosis in a population cohort.

Methods: This retrospective, cross-sectional study included 8,545 participants who underwent magnetic resonance elastography (MRE) at 13 nationwide health-promotion centers during a routine health check-up. At-risk group was mainly defined as the group of individuals with any of the following risk factors: fatty liver, two or more metabolic abnormalities, diabetes mellitus, and abnormal liver function test based on various guidelines. The area under the receiver-operating characteristic (AUROC) curves of FIB-4 and NFS were compared using DeLong's test.

Results: Considerable subjects (28.2~39.6%) of 'at-risk group' did not combine with NAFLD. 'At-risk group' without NAFLD had more favorable metabolic profiles, such as lower waist circumference, BMI, and serum triglyceride and glucose levels. But the prevalence of advanced fibrosis in the at-risk group without NAFLD was higher than that in the at-risk group with NAFLD. Proportion of 'at risk group' according to various guidelines was somewhat diverse (67.4~80.2%) in population-based cohort without risk of viral or alcoholic liver disease. The prevalence of advanced hepatic fibrosis (≥F3) in the 'at risk-group' was 2.3%~2.8%. The AUROC of FIB-4 for diagnosing advanced fibrosis in various 'average risk group' was good (0.832~0.837). The AUROC of FIB-4 and NFS in NAFLD group were similar. However, diagnostic performance of FIB-4 was higher than that of NFS in various 'at risk group' definitions.

Conclusions: Proportion of 'at risk group' according to various guideline was somewhat diverse. But the prevalence of advanced hepatic fibrosis suggested by various guidelines was similar and diagnostic performance of FIB-4 in 'at-risk group' was good.

Keywords: Nonalcoholic fatty liver disease, Fibrosis, Fibrosis-4 index, Screening

PE-281

Management of Chemotherapy Induced Paranasal Sinus Fistula in Mantle Cell Lymphoma

Sathya Veera Merla, Harshita Dubey, Amar Ranjan

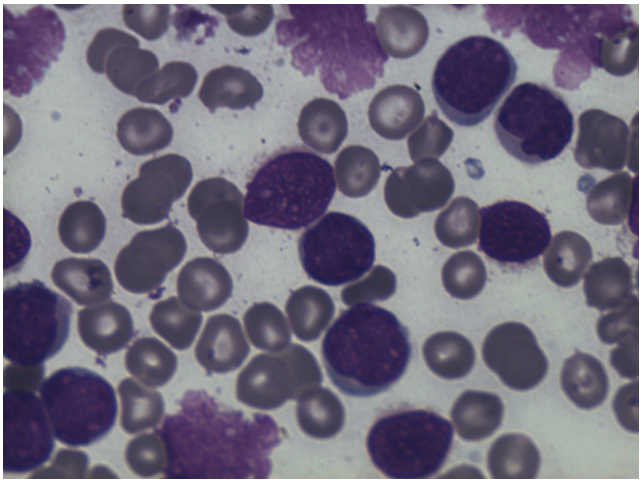
All India Institute of Medical Sciences, New Delhi, India

Aims: A fistula is formed between maxillary sinus and oral cavity following surgery. Spontaneous healing may occur if the diameter is lesser than 2 mm, while larger one needs immediate management to avoid sinusitis. MCL of paranasal sinuses are prone to develop oro-antral fistula, as described below.

Methods: Case study

Results: A case of 59 yr elderly male presented with complaint of nasal blockade along with watery discharge from left eye for 8 months. CT scan showed polypoidal mucosal thickening in B/L maxillary/ethmoidal/sinusoisal/ sinus. PET-CT showed low grade FDG uptake in enlarged lymph nodes. Viral markers were negative. Total leukocyte count showed leukocytosis (15320/ul). Abnormal lymphoid cell in BMA and PS were 70% & 20% respectively. Bone marrow biopsy showed lymphoid cells positive for CD20, CD5, CD23 & Cyclin D1 and negative for CD3. Biopsy of polupoidal mass showed atypical lymphoid cells which were LCA+, CD20+, CD5 +, BCL2+, CYCLIND1+, KI67: 70-80%. A diagnosis of Mantle Cell Lymphoma (MCL) stage IV with MIPI- intermediate risk was considered. T/T with BR regime #6 cycles showed partial Response. Now he developed

paraesthesia in right upper limb. Rituximab (R-mab) as maintenance therapy was started. After 3 cycles, he developed regurgitation of food from paranasal sinus fistula along with infraorbital edema of left eye. The fistula was managed conservatively. After 10# R-mab, Treatment Free Interval of 23 months was seen. Later the patient developed subcutaneous swellings in right subscapular region measuring 5x6cm, at C7 vertebra level 2x3cm and at left sided anterior abdominal wall 1x1cm. Testicles were normal. PET scan showed increased uptake in swellings of scapular, suboccipital region and chest as well as abdominal wall. Right lung lesion was s/o Tree in bud appearance s/o infective pathology. RCHOP was given. The patient is on follow up.



Conclusions: Repairing oro-antral defects is a challenging task. It is managed by creating a barrier using local soft tissue.

Keywords: Chemotherapy, Paranasal sinus fistula, Mantle cell lymphoma

PE-282

Drug Induced Liver Injury Combined with Severe Cutaneous Adverse Drug Reaction Caused by Celecoxib

Jae Jin Lee, Jeong Eun Song

Department of Internal Medicine, Daegu Catholic University School of Medicine

Aims: The liver and skin are the organs most commonly involved in serious adverse drug reactions. Rarely a drug reaction can affect both organs concurrently. The association of drug-induced liver injury (DILI) and Stevens-Johnson syndrome (SJS) or toxic epidermal necrosis (TEN) is even rarer.

Methods: A 53-years old woman visited our hospital presenting with jaundice. She had no underlying disease. She had been taking celecoxib due to arthritis for 4 weeks before visiting our hospital. The initial liver function test (LFT) results were elevated as follows; aspartate aminotransferase was 186 U/L, alanine aminotransferase was 33 U/L, alkaline phosphatase was 1101 U/L, and total bilirubin was 32.4 mg/dL. An R ratio of 0.55 confirmed cholestatic pattern of liver injury, and both anti-mitochondrial antibody and imaging study for bile duct obstruction showed no specific findings. In consideration of the possibility of DILI caused by celecoxib, the administration of celecoxib was promptly discontinued. On the third day of hospitalization, diffuse cutaneous erythematous patches, large bullae had developed on the abdomen, back and both legs, and later progressed to skin detachment, oral mucositis and ocular lesion. Skin biopsy was done for cutaneous lesion, and the histologic examination was confirmed with TEN. After administration of intravenous methylprednisolone and intravenous immunoglobulin, the cutaneous lesions gradually improved. After improvement of the skin lesions, we performed a liver biopsy, and pathological results showed acute cholestatic hepatitis, consistent with toxic hepatitis.

Results: Based on the RUCAM scale and LiverTox, we diagnosed the cause of cholestatic liver injury as DILI due to celecoxib. Additionally, we conducted a literature review and found data on celecoxib-induced DILI and severe adverse skin reactions. She is currently under conservative treatment, and if liver function dose not recover and progresses to chronic cholestatic hepatitis, liver transplantation is being considered.

Conclusions: Although co-occuurence of DILI and TEN due to celecoxib is rare, it is known that the mortality rate is significant high. Prompt diagnosis and discontinuation of the culprit agent are key in recovery which may take weeks to months. Close monitoring under multispecialty teams should be guaranteed to guide treatment and resolve complications.

Keywords: Drug induced liver injury, Celecoxib, Toxic epidermal necrolysis

PE-283

Liver Transplantation due to Chronic Hepatic Graft-versus Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation : Case Series of 3 Patients

Jae-Sung Yoo[1], Woo Tae Cho[3], Young-Kyoung You[2], Ho Joong Choi[2], Jeong Won Jang[1], Jong Young Choi[1], Pil Soo Sung[1*]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [2]Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, [3]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Aims: Cases of liver transplantations (LT) due to the progression of graft-versus-host disease (GVHD) following hematopoietic stem cell transplantation (HSCT) are rare. To date, there have been 3 cases of these events at Seoul St. Mary Hospital.

Methods: The first patient was a 61-year-old male with myelodysplastic syndrome (MDS) who underwent HSCT. He had suffered from chronic liver GVHD for over 2 years. On post-HSCT day 654 (D+654), he visited the hospital with abdominal distension. Abdominal computed tomography (CT) revealed liver cirrhosis with massive ascites. Despite the use of diuretics and repeated paracentesis, the ascites remained uncontrolled. To address the intractable ascites, LT was performed. After the operation, uncontrolled infections such as pneumonia and bacteremia continued. As the septic condition progressed, the patient passed away.

Results: The second case involved a patient on post-HSCT day 177

(D+177) from a sibling donor due to acute myeloid leukemia (AML). The 57-year-old patient showed a sudden elevation of total bilirubin levels to above 8 mg/dL, along with poor oral intake and general weakness. Abdominal sonography revealed no structural abnormalities. Liver histopathology indicated chronic GVHD with a moderate degree of porto-periportal inflammatory activity and infiltration of eosinophils and neutrophils in the porto-periportal and sinusoidal areas. Despite steroid pulse therapy and immune-suppressive therapy (IST), the bilirubin level gradually increased to 20 mg/dL. At post-HSCT day 270 (D+270), LT was carried out using the same donor. Following LT, the bilirubin levels dramatically decreased. The third case involved a 65-year-old male patient with MDS who underwent HSCT from a sibling donor. About 3 months after hematopoietic stem cell transplantation, total bilirubin was within the range of 1 to 3 mg/dL, but alkaline phosphatase and gamma-glutamyl transferase rose to 600 and 2000, respectively. As GVHD became chronic, decompensated symptoms such as esophageal varix and ascites occurred repeatedly. At post-HSCT day 2949 (D+2949), LT was performed. The liver donor was his son, different from the HSCT donor. After LT, liver function tests were restored, and the decompensated symptoms disappeared.

Conclusions: LT was performed in various clinical situations after HSCT, and the prognosis was not always good. Chronic GVHD could also progress to decompensated cirrhosis, even if it was persistent, and eventually lead to a situation requiring LT.

Keywords: Liver transplantation, Graft-versus host disease, Allogeneic hematopoietic stem cell transplantation

PE-284

Implemented Responses of Viral Hepatitis Elimination in Mongolia

D. Badral, J. Nyamsuren, Ch. Munkhtsetseg, E. Nyambayar, J. Baigalmaa

National Center for Communicable Diseases, Mongolia

Aims: Implemented responses to address viral hepatitis as a public health threats.

Methods: To address this public health threats, the Healthy liver program (HLP) was implemented between 2017-2021 years to combat viral hepatitis and embarked on ambitious criteria as global goals.

Results: Mongolia has some of the highest rates of viral hepatitis prevalence in the world with 9.3% for hepatitis C virus and 7.8% for HBsAg infections as of 2021, and following, the high burden prevalence of liver cirrhosis and liver cancer which most of them diagnosed at a late stage. To address these public health threats, the Healthy liver program (HLP) was implemented between 2017-2021 years to combat viral hepatitis and embarked on ambitious criteria as global goals (defined as a 90% reduction in incidence and 65% reduction in mortality). The HLP have successfully implemented by supporting Governance decision based Health Insurance with aims to control hepatitis B virus and eliminate hepatitis C virus as a public health threat by 2020 by screening 80% of the population 15 years of age and over, treating 80% of those eligible, and achieving 90% viral suppression or cure. Otherwise it is population based given opportunity mass screening the whole population to identify prevalence of these infections. Therefore, the Ministry of Health has approved the HLP to continue with 34 different actions and 15 national criteria in four goals during 2022-2025 years. Additionally, one of seven countries across the six WHO regions, Mongolia has piloted a pre-assessment for validation of viral hepatitis elimination in 2022 to defining a path to elimination and updating the interim guidance for the validation of elimination of viral hepatitis as a public health threat and for us to understand experience and gaps, and it was crucial to address the way forward. For chronic surveillance, cascade of care of viral hepatitis diagnosis and treatment is important to strengthen the national data system, however there is no online electronic system in the surveillance department nationwide. Furthermore, Mongolia has assessed the situation analysis on establishing hospital based sentinel surveillance of viral hepatitis sequelae including liver cirrhosis, cancer, and death and developing guidance on sequelae surveillance for liver cirrhosis and liver cancer caused by viral hepatitis.

Conclusions: In summary, the prevalence and incidence rate of viral hepatitis infection is decreasing year by year in Mongolia. Cascade of viral hepatitis diagnosis and treatment could be monitored and addressed in order to reach the HLP goals by 2025 in Mongolia.

Keywords: Viral hepatitis, Prevalence, Surveillance

PE-285

Liver-Directed Combined Radiotherapy in Locally Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

Jina Kim[1], Jason Chia-Hsien Cheng[2], Taek-Keun Nam[3], Jinhee Kim[4], Byoung Kuk Jang[5], Wen-Yen Huang[6], Hiroshi Aikata[7], Myungsoo Kim[8], Jung Hyun Kwon[9], Jinbo Yue[10], Victor H.F. Lee[11], Zhao Chong Zeng[12], Jinsil Seong[1]

[1]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea [2]Department of Radiation Oncology, National Taiwan University Hospital, Taipei, Taiwan [3]Department of Radiation Oncology, Chonnam National University Hwasun Hospital, Hwasun, Korea [4]Department of Radiation Oncology, Keimyung University School of Medicine, Daegu, Korea [5]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea [6]Department of Radiation Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan [7]Department of Gastroenterology, Hiroshima Prefectural Hospital, Hiroshima, Japan [8]Department of Radiation Oncology, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea [9]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea [10]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China [11]Department of Clinical Oncology, The University of Hong Kong, Hong Kong, China [12]Department of Radiation Oncology, Zhongshan Hospital Affiliated to Fudan University, Shanghai, China

Aims: Although systemic treatment is the mainstay for advanced hepatocellular carcinoma (HCC), numerous studies have highlighted the added value of local treatment. This study aimed to investigate the clinical efficacy of liver-directed combined radiotherapy (LD-CRT) compared with that of sorafenib, a recommended treatment until recently for locally advanced HCC presenting portal vein tumor thrombosis (PVTT), using a multinational patient cohort.

Methods: We identified patients with HCC presenting PVTT treat-

ed with either sorafenib or LD-CRT in 10 tertiary hospitals in Asia from 2005 to 2014. Propensity score matching (PSM) was performed to minimize the imbalance between the two groups. The primary endpoint was overall survival (OS), and secondary endpoints were progression-free survival (PFS), and treatment-related toxicity.

Results: A total of 1,035 patients (675 in the LD-CRT group and 360 in the sorafenib group) were included in this study. After PSM, 305 patients from each group were included in the analysis. At a median follow-up of 22.5 months, the median OS was 10.6 and 4.2 months for the LD-CRT and sorafenib groups, respectively (p<0.001). Conversion rate to curative surgery was significantly higher (8.5% vs. 1.F0%, p<0.001) while grade ≥ 3 toxicity was fewer (9.2% vs. 16.1%, p<0.001) in the LD-CRT group.

Conclusions: LD-CRT improved survival outcomes with a higher conversion rate to curative surgery in patients with locally advanced HCC presenting PVTT. Although further prospective studies are warranted, active multimodal local treatment involving radiotherapy is suggested for locally advanced HCC presenting PVTT.

Keywords: Hepatocellular carcinoma, Portal vein tumor thrombosis, Sorafenib, Radiotherapy

PE-286

Effectiveness of Transarterial Chemoembolization for Early Hepatocellular Carcinoma: Single-Center Experience

Hyun Phil Shin, Moon Hyung Lee

Department of Gastroenterology, Kyung Hee University Hospital at Gangdong, Seoul, Korea

Aims: Surgical resection or ablation treatment is first recommended as treatment of choice in patients with early hepatocellular carcinoma, but transarterial chemoembolization (TACE) is performed due to other medical condition. This is the study to evaluate the efficacy of TACE in patients with early stage hepatocellular carcinoma (HCC).

Methods: A retrospective analysis was performed for all TACE procedures done at Kyung Hee University Hospital at Gangdong, during a 15-year period (July 2006-November 2021). Patients with solitary tumors ≤5 cm were included.

Results: Ninety-seven eligible patients were included. The mean participant age was 63.47±11.02 years, and 69 patients were males (71.1%). The number of Child A patients was the highest (74 patients [76.3%]), followed by Child B (19 patients [19.6%]) and Child C (4 patients [4.12%]). Complete response was achieved in 84 (86.6%) patients after 1st TACE procedures. overall survival rates at 1, 2, and3 years were 91.8%, 87.3%, and 75.4%, respectively. In multivariate analysis, the patients with AFP >20 showed statistically related to overall survival (p=0.04).

Conclusions: TACE is for treating early HCC patients, who are unsuitable for ablation or resection, and may result comparable survival benefit. It can also be used as a bridge therapy before curable treatment for these patients.

Keywords: Effectiveness, Transarterial chemoembolization, Hepatocellular carcinoma, Early stage

유한양행의 **로수바미브**는
한국인 제2형 당뇨병 환자를 대상으로 한 연구*에서
지질 프로파일 개선의 유효성과 안전성을 입증했으며,
국내에서 **연간 100만 건 이상 처방**§되고 있습니다.

* Diabetes Ther. 2020 Apr;11(4):859-871(rosuvastatin 10mg monotherapy 대비 로수바미브 10/5mg의 유효성과 안전성을 확인). § 2022년 유비스트 '로수바미브정' 처방건 수 기준

전문의약품

로수바미브정(에제티미브/로수바스타틴칼슘) 10/5mg, 10/10mg, 10/20mg [원료약품 및 분량] • 로수바미브 10/5mg : 에제티미브(USP) 10.0mg, 로수바스타틴칼슘(벌규) 5.2mg(로수바스타틴으로서 5mg) • 로수바미브 10/10mg : 에제티미브(USP) 10.0mg, 로수바스타틴칼슘(벌규) 10.4mg(로수바스타틴으로서 10mg) • 로수바미브 10/20mg : 에제티미브(USP) 10.0mg, 로수바스타틴칼슘(벌규) 20.8mg(로수바스타틴으로서 20mg) **[성상]** • 로수바미브 10/5mg : 분홍색의 장방형 필름코팅정 • 로수바미브 10/10mg : 노란색의 장방형 필름코팅정 • 로수바미브 10/20mg : 분홍색의 달걀형 필름코팅정 **[효능 · 효과]** 원발성 고콜레스테롤혈증; 원발성 고콜레스테롤혈증(이형접합 가족형 및 비가족형) 또는 혼합형 이상지질혈증 환자의 상승된 총 콜레스테롤(totalC), LDL-콜레스테롤(LDL-C), 아포 B 단백(Apo B), 트리글리세라이드(TG) 및 non-HDL-콜레스테롤을 감소시키고, HDL-콜레스테롤(HDL-C)을 증가시키기 위한 식이요법의 보조제로서 이 약을 투여합니다. 고콜레스테롤혈증에 기인한 동맥경화성 혈관 질환의 위험성이 증가한 환자에게 지질조절약물을 투여할 때에는 많은 위험 인자를 고려해야 합니다. 지질조절약물은 적절한 식이요법(포화지방 및 콜레스테롤 제한을 포함)과 함께 사용하고, 식이요법 및 다른 비약물학적 조치에 대한 반응이 불충분한 경우에 사용해야 합니다. 이 약 투여에 앞서 이상지질혈증의 다른 이차적 원인(예를 들면, 당뇨, 갑상선기능저하증, 폐쇄성 간질환, 만성 신부전, LDL-콜레스테롤을 증가시키는 약물 및 HDL-콜레스테롤을 감소시키는 약물[progestin, anabolic steroid, 및 corticosteroid])을 확인하여야 하며, 필요한 경우 이차적 원인을 치료해야 합니다. 지질 검사시에는 총콜레스테롤, LDL-콜레스테롤, HDL-콜레스테롤 및 트리글리세라이드를 포함해야 합니다. 트리글리세라이드 수치가 400mg/dL 이상(4.5mmol/L 이상)인 경우에는 초원심분리로 LDL-콜레스테롤 농도를 측정해야 합니다. 급성 관상동맥 사고로 입원할 경우에는 입원 시 혹은 입원 후 24시간 이내에 지질을 측정해야 합니다. 환자의 퇴원 전 혹은 퇴원 시에 LDL 저하치료를 시작하는데 있어 이 측정치가 참고가 될 수 있습니다. **[용법·용량]** 이 약은 식사와 관계없이 1일 1회 투여합니다. 이 약을 투여하기 전 또는 투여 중인 환자는 반드시 표준 콜레스테롤 저하식을 지속적으로 해야 합니다. 이 약의 투여량은 환자의 LDL-콜레스테롤의 기저치, 권장되는 치료목표치 및 환자의 반응에 따라 조절되어야 합니다. 원발성 고콜레스테롤혈증: 이 약의 용량범위는 1일 10/5mg~10/20mg입니다. 초회용량으로 1일 10/5mg이 권장됩니다. LDL-콜레스테롤 감소가 더 많이 요구되는 환자의 경우 용량을 조절하여 투여할 수 있습니다. 이 약의 투여를 시작한 후 또는 용량을 적정한 후에는 4주 이상의 간격을 두고 혈중 지질 수치를 확인한 후 그에 따라 용량을 조절하며, 1일 최대 10/20mg까지 증량할 수 있습니다. 에제티미브와 로수바스타틴을 병용으로 복용하고 있는 환자인 경우, 복용의 편리함을 위하여 이 약(개개의 주성분 함량이 동일한 복합제)으로 전환할 수 있습니다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 마십시오. 1) 이 약의 주성분 또는 구성성분에 과민반응이 있는 환자 2) 활동성 간질환 환자 또는 혈청 아미노전달효소 수치가 원인불명으로 지속적으로 높은 증상을 수반한 환자('5. 일반적 주의' 참조) 3) 근질환 환자 4) 사이클로스포린 병용투여 환자 5) 중증의 신부전의 신장애 환자(creatinine clearance (CLcr)<30mL/min) 6) 임부 또는 임신하고 있을 가능성이 있는 여성 및 수유부 ('7. 임부 및 수유부에 대한 투여' 참조) 7) 근병증/횡문근융해증에 걸리기 쉬운 환자들에게 로수바스타틴 40밀리그램 용량 투여는 금기입니다. 이러한 인자들은 아래와 같습니다. (1) 중등도의 신장애 (크레아티닌 청소율 < 60ml/min) (2) 갑상선기능저하증 (3) 유전적인 근질환 병력 또는 가족력이 있는 경우 (4) 다른 스타틴계 약물(HMG-CoA 전환효소 저해제) 또는 피브레이트 계열 약물에 대한 근육 독성의 병력이 있는 경우 (5) 알코올 중독 (6) 혈장 농도가 증가할 수 있는 상황 (7) 아시아계 환자 (8) 피브레이트 계열 약물 병용투여 8) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 됩니다.자세한 내용은 제품설명서 참조) **[저장방법]** 기밀용기, 실온(1~30℃) 보관 **[포장단위]** 30정(PTP), 100정(병) **[개정연월일]** 22.10.21 ※ 제품에 대한 자세한 내용은 최신의 제품설명서 또는 식약처 의약품통합정보시스템 홈페이지(https://nedrug.mfds.go.kr/)를 참조하여 주시기 바랍니다.

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유한양행

레코미드® 서방정
Rebamipide 150mg

Reference) 1. 레코미드® 서방정 제품 설명서(개정연월일 2020.12.16)

레코미드® 서방정(rebamipide) 제품요약정보

[전문의약품]

[원료약품 및 분량] 유효성분 : 레바미피드 150mg **첨가제** : 스테아르산마그네슘, 유당수화물, 콜로이드성이산화규소, 히드록시프로필셀룰로오스, 히프로멜로오스 **[효능·효과]** 다음 질환의 위점막병변(미란, 출혈, 발적, 부종)의 개선 : 급성위염, 만성위염의 급성악화기 **[용법·용량]** 성인 1 일 2 회, 아침 저녁으로 1 회 1 정씩 복용 이 약을 통째로 삼켜야 하며, 나누어 복용하거나 씹으면 안된다. **[사용상의 주의사항] 1. 다음 환자에는 투여하지말것** 1) 이 약 성분에 과민반응 병력 환자 2) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. **2. 이상반응 : 1) 이 약에서 보고된 이상반응** 이 약에 대한 안전성은 급성 또는 만성 위염 환자를 대상으로 2주간의 무작위배정, 이중눈가림, 활성대조(대조약 : 레바미피드 속방정) 임상시험(n= 470)에서 평가되었다. 이상반응은 이 약 투여군에서 24명(10.17%), 대조약 투여군에서 20명(8.55%)에서 발생하였다. 가장 빈번하게 발생한 이상반응은 이 약 투여군에서 위장관계 장애 5명(2.12%), 감염 및 기생 4명(1.69%), 근골격계 및 결합조직 장애 3명(1.27%)이었으며, 대조약 투여군에서는 감염 및 기생 6명(2.56%), 위장관계 장애 5명(2.14%)이었다. 이상반응 중 임상시험용의약품과 인과관계가 있는 것으로 판단된 약물이상반응(ADR)은 이 약 투여군에서 17명(7.2%), 대조약 투여군에서 12명(5.13%) 발생하였다. 가장 빈번하게 발생한 약물이상반응은 이 약 투여군에서는 위장관계 장애 4명(1.69%), 대조약 투여군에서는 위장관계 장애 3명(1.28%)이었다. 두 치료군에서 가장 빈번하게 발생한 약물이상반응인 위장관계 장애의 중등도는 모두 경증이었다. 두 치료군에서 중대한 이상반응은 발생하지 않았다. 영구 투여중단을 초래한 약물이상반응은 대조약 투여군에서 어지러움 1건(0.42%)이 보고 되었다. **[저장방법]** 기밀용기, 실온(1-30℃)보관 **[사용기간]** 제조일로부터 36 개월 **[포장단위]** 30 정/병, 300 정/병 **[제조·판매자]** (주)유한양행 **[개정연월일]** 2020.12.16

※ 자세한 허가사항은 식약처 의약품통합정보시스템 홈페이지(https://nedrug.mfds.go.kr/)를 참조하여 주시기 바랍니다. 요약 허가사항에 반영되지 않은 허가 변경이 상기일자 이후에 있을 수도 있습니다.

RCS-A1.0-001-202101

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References 1. 2018 대한간학회 만성 B형 간염 진료 가이드라인 2. Oh H, et al. Aliment Pharmacol Ther 2020;52:371-81. 3. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection 4. Terrault NA, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560-1599.

베믈리디®정 (테노포비르알라페나미드헤미푸마르산염)

[수입자] 길리어드 사이언스 코리아(유), 서울특별시 중구 을지로5길 26 센터원빌딩 서관 15층 (대표전화: 02-6030-3300, 제품관련문의: 0079-814-800-9172 (수신자 부담))

* 처방하시기 전에 반드시 허가사항 전문을 확인하여 주시기바랍니다. 최신 허가사항은 아래 QR 코드를 통해 확인하실수 있으며, 길리어드사이언스코리아 홈페이지(www.gilead.co.kr) 또는 식품의약품안전처 의약품통합정보 시스템 (http://nedrug.mfds.go.kr) 에서도 보실 수 있습니다.)

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KR-VEM-0185_v1.0(29/August/2023)

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Warnings** 1) Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV, who were not receiving HBV antiviral therapy: Test for evidence of HBV infection before initiating HCV treatment. Monitor for signs of hepatitis flare or HBV reactivation. 2) Serious Symtomatic Bradycardia When Coadministered with Amiodarone: Coadministration of amiodarone with this drug is not recommended. (Refer to full PI for more information)**2. Do not administer in the following situations** 1) This drug and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated. 2) In combination with ribavirin, pregnant women and their partners, or women of childbearing potential. 3) Patients who are hypersensitive to the active substances or to any of the excipients.**3. Adverse Reactions** Subjects without Cirrhosis or with Compensated Cirrhosis: From three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects who received this drug for 12 weeks, the most common adverse reactions (at least 10%) were headache and fatigue. Adverse reactions, all grades, observed in greater than or equal to 5% in ASTRAL-1 include headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). The adverse reactions observed in subjects treated with this drug in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Subjects with Decompensated Cirrhosis: In Phase 3 trial (ASTRAL-4) including 87 subjects who received this drug with ribavirin for 12 weeks, the most common adverse reactions (all grades with frequency of 10% or greater) were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Less Common Adverse Reactions Reported in Clinical Trials: rash, depression (Refer to full PI for more information) **4. General Precautions** 1) Risk of reduced therapeutic effect due to concomitant use of this drug with inducers of P-gp and/or moderate to strong inducers of CYP. 2) Refer to the ribavirin prescribing information for risks associated with ribavirin and this drug combination treatment **5. Drug interactions** 1) Drugs that are inducers of P-gp and/or moderate to strong inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of this drug, leading to reduced therapeutic effect. 2) Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Coadministration of this drug with drugs that are substrates of these transporters may increase the exposure of such drugs. (Refer to full PI for more information)**6. Use in Pregnant Women and Nursing Mothers** 1) Pregnancy: If this drug is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. 2) Lactation: It is not known whether the components of this drug are present in human breast milk, affect human milk production, or have effects on the breastfed infant. 3) If this drug is used in combination with ribavirin, special care should be taken to avoid pregnancy in female patients and female partners of male patients.**7. Use in Specific Populations** 1) The safety and effectiveness of this drug have not been established in pediatric patients less than 12 years of age. 2) No dosage adjustment of this drug is warranted in geriatric patients. 3) No dosage adjustment of this drug is required for patients with mild, moderate, or severe renal impairment, including ESRD requiring dialysis. 4) No dosage adjustment of this drug is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). **[Storage Condition]** Store in a tight container at room temperature (1~30°C) **[Package Unit]** 28 tablets **[Importer]** Gilead Sciences Korea Ltd., West Tower 15F, Center 1, 26, Euljiro 5-gil, Jung-gu, Seoul, Korea (Representative phone: 02-6030-3300, Medical information: 0079-814-800-9172) **[Date of Preparation]** 2022.02.17 (EPC-2202-01) ※ Please refer to full prescribing information (www.gilead.co.kr or nedrug.mfds.go.kr) before prescription for detailed information. This abridged PI might not include some latest information after the date below.

*Adults treated with SOF/VEL 400/100 mg, without ribavirin, were included. All HCV patients reaching Week 12 or 24 post-treatment were assessed for SVR12/24. Factors associated with not achieving SVR12/24 for virological reasons were evaluated using logistic regression analysis. Overall, 5552 patients were included: 13.3% treatment-experienced; 20.7% compensated cirrhotic; 30.2% genotype 1; 29.5% genotype 2; 32.9% genotype 3; 4.7% genotype 4; 3.7% HIV coinfection; 13.4% current/former intravenous drug use. SVR12/24 in the effectiveness population (n = 5,196; excluding patients who did not achieve SVR12/24 due to non-virologic or unknown reasons) was 98.9%. SVR12/24 in the overall population was 92.6%. All patients with unknown genotype (n = 42), unknown fibrosis score (n = 82) and unknown treatment history (n = 33) achieved SVR12/24 with Epclusa® for 12 weeks. The low discontinuation (<2%) and LTFU rates (4%) in this real-world analysis are consistent with previous clinical studies. Additionally, where information was available, few of the discontinuations were due to adverse events linked to SOF/VEL therapy, which is consistent with the Phase 3 data. This underlines the favourable safety and tolerability profile of SOF/VEL as a protease inhibitor-free DAA, as also shown previously in clinical trials.[1]

†Epclusa® monotherapy for 12 weeks in previously treatment-naïve and treatment-experienced patients without cirrhosis or with compensated cirrhosis (Child-Pugh A). Epclusa®+ribavirin combination therapy for 12 weeks in previously treatment-naïve and treatment-experienced patients with decompensated cirrhosis (Child-Pugh B or C).

‡Pediatric patients aged 12 years or older or weighing 30 kg or more

AE, adverse event; **DAA,** direct acting antiviral; **HCV,** hepatitis C virus; **HIV,** Human Immunodeficiency Virus; **PI,** protease inhibitor; **SOF,** sofosbuvir; **SVR12/24,** sustained virological response 12/24 weeks after the end of treatment; **VEL,** velpatasvir

Reference 1. Mangia A, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: Analysis of 5,552 patients from 12 cohorts. Liver Int 2020;40:1841 - 52.**2.** Epclusa® Prescribing Information, 2022.

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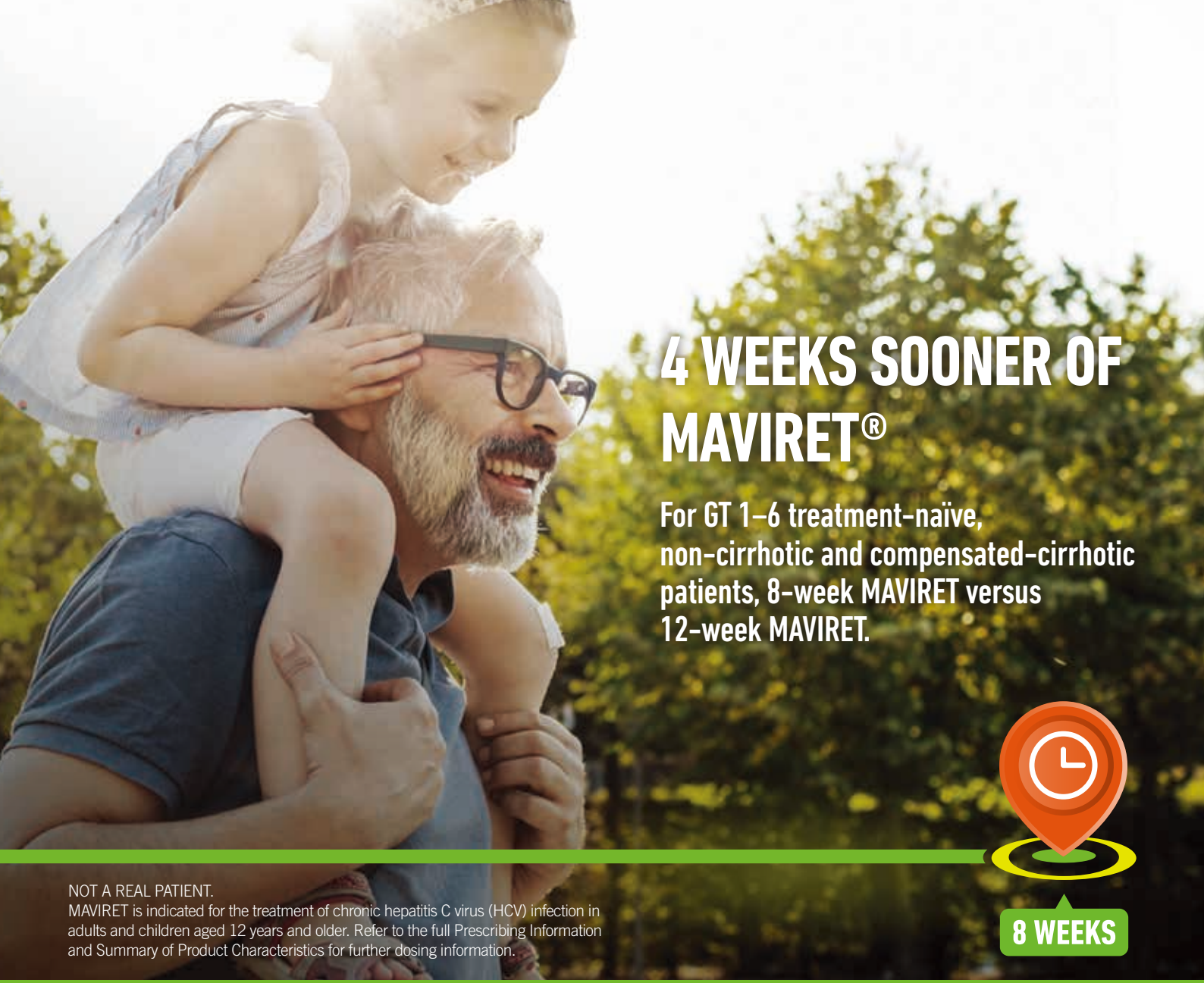
GILEAD YUHAN

KR-EPC-0170_v1.0(4/May/2025)



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For GT 1–6 treatment-naïve, non-cirrhotic and compensated-cirrhotic patients, 8-week MAVIRET versus 12-week MAVIRET.

8 WEEKS

NOT A REAL PATIENT.
MAVIRET is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults and children aged 12 years and older. Refer to the full Prescribing Information and Summary of Product Characteristics for further dosing information.

마비렛®정 제품요약정보

[효능·효과] 만성 C형 간염 바이러스(hepatitis C virus; HCV) 유전자형 1, 2, 3, 4, 5, 또는 6 형에 감염된 성인 및 만 12세 이상 청소년 환자의 치료 **[용법용량]** 이 약은 글레카프레비르와 피브렌타스비르가 함유된 고정 용량 복합 정제이다. 이 약의 권장 경구 투여 용량은 1일 1회 동일한 시간에, 3정을 음식과 함께 복용하는 것이다. 이 약은 씹거나, 부수거나, 자르지 말고 통째로 삼켜야 한다. 표 1과 2에 간경변을 동반하지 않거나 대상성 간경변을 동반하고 신장애(투석 환자 포함)가 있거나 없는 HCV 단독 감염 환자 집단 및 HCV/HIV-1 동시 감염 환자 집단에 근거한 이 약에 대한 권장 치료 기간이 제시되어 있다.

표 1. 치료 경험이 없는 환자들에 대한 권장 치료 기간

유전자형	권장 치료 기간	
	간경변 없는 경우	대상성 간경변 있는 경우
1, 2, 3, 4, 5, 6형	8주	8주

표 2. 치료 경험이 있는 환자들에 대한 권장 치료 기간

유전자형	이전 치료 경험	권장 치료 기간	
		간경변 없는 경우	대상성 간경변 있는 경우
1, 2, 4, 5, 6형	인터페론, 페그인터페론, 리바비린 및/또는 소포스부비르	8주	12주
1형	이전 NS5A 저해제 치료경험이 없고, NS3/4A 단백분해효소 저해제1 치료경험이 있을 경우	12주	
	이전 NS3/4A 단백분해효소 저해제 치료경험이 없고, NS5A 저해제2 치료경험이 있을 경우	16주	
3형	인터페론, 페그인터페론, 리바비린 및/또는 소포스부비르	16주	

1. 임상시험에서, 시메프레비르 및 소포스부비르 또는 시메프레비르, 보세프레비르 또는 텔라프레비르와 페그인터페론 및 리바비린의 병용요법으로 투여받음
2. 임상시험에서, 레디파스비르 및 소포스부비르 또는 다클라타스비르와 페그인터페론 및 리바비린의 병용요법으로 투여받음

간장애 환자에 대한 투여: 경증 간장애(Child-Pugh A)가 있는 환자들의 경우, 이 약의 용량 조절은 필요하지 않다. 이 약은 중등증 또는 중증 간장애(Child-Pugh B 또는 C) 또는 비대상성 간경변(hepatic decompensation) 병력이 있는 환자에게는 투여 금기이다. 신장애 환자에 대한 투여: 경증, 중등증 또는 투석을 받고 있는 환자를 포함한 중증 신장애 환자에서 이 약의 용량 조절은 필요하지 않다. 간 또는 신장 이식 환자에 대한 투여: 이 약은 간 또는 신장 이식 환자에 12 주 동안 투여할 수 있다. 이전 NS3/4A 단백분해효소 저해제 치료경험이 없고, NS5A 저해제 치료경험이 있는 유전자형 1 형, 인터페론, 페그인터페론, 리바비린 및/또는 소포스부비르 치료 경험이 있는 유전자형 3 형의 이식환자에서는 16 주의 치료기간을 고려해야 한다. (용법용량 표 2 및 11. 전문가를 위한 정보 2) 임상시험 정보 항 참고) 약물 복용을 놓친 경우: 약물 복용을 놓치고: • 일반적으로 이 약을 복용하는 시간으로부터 18시간 이하 경과한 경우 - 환자에게 해당 용량을 즉시 복용하고, 다음 용량을 원래 복용하던 시간에 복용하도록 조언한다. • 일반적으로 이 약을 복용하는 시간으로부터 18시간 초과 경과한 경우 - 환자에게 놓친 용량을 복용하지 말고 다음 용량을 원래 복용하던 시간에 복용하도록 조언한다. **[주요 사용상 주의사항] 1. 경고** B형 간염 재활성화 위험: HBV/HCV 동시 감염 환자에서 B형 간염 바이러스(hepatitis B virus; HBV) 재활성화 사례(일부에서 간부전이나 사망이 유발됨)가 HCV에 직접 작용하는 항바이러스제로 치료하는 동안 보고되었다. HBV 재활성화는 혈청 HBV DNA 수치 증가로 발현되는 급작스런 HBV 복제 증가가 특징이다. HBV 감염이 해결된 환자들(HBsAg 음성이고 항-HBc 양성)에서, HBsAg가 다시 나타날 수 있다. HBV가 재활성화되면 종종 간기능 검사 수치 이상(즉, 아미노기 전이효소 및/또는 빌리루빈 수치 상승)이 나타날 수 있으며 심할 경우 간부전 또는 사망이 유발될 수 있다. 치료를 시작하기 전에 모든 환자에 대하여 HBV 선별검사를 실시해야 한다. 현재 또는 이전 HBV 감염 환자는 이 약의 치료 중 및 치료 후 간염의 급성 악화(hepatitis flare) 또는 재활성화 확인을 위해 임상적 및 실험실학적 검사(예, HBsAg, HBV DNA, ALT, 빌리루빈 등)로 주기적으로 모니터링해야 한다. HBV의 재활성화가 나타난 경우, 전문가와 상의한다. 당뇨병 환자에서의 사용: 당뇨병 환자는 HCV에 직접 작용하는 항바이러스 치료를 시작한 후, 포도당 조절이 개선되어 잠재적으로 증상이 있는 저혈당을 경험할 수 있다. 직접 작용하는 항바이러스제 치료를 시작하는 당뇨병 환자의 혈당 수준을 특히 처음 3개월 동안 면밀히 모니터링 해야 하며, 필요 시 당뇨병 치료제를 수정해야 한다. 직접 작용하는 항바이러스제 치료가 시작될 때 환자의 당뇨 관리 담당 의사에게 알려야 한다. 간질환이 진행된 환자의 비대상성 간경변/간부전 위험: 이 약을 포함한 HCV NS3/4A 단백질분해효소억제제 함유 요법으로 치료받은 환자에서 치명적인 결과를 가진 환자를 포함하여 비대상성 간경변 및 간부전의 시판 후 사례가 보고되었다. 이러한 사례는 특정할 수 없는 집단에서 자발적으로 보고된 것이었기 때문에, 신뢰할 수 있는 해당 사례의 발생빈도나 약물의 노출과의 상관관계를 확인하는 것이 모두 가능하지는 않았다. 중증의 결과를 보이는 환자의 대다수는 이 약으로 치료를 시작하기 전에 중등증 또는 중증 간 장애(Child-Pugh B 또는 C)로 진행된 간 질환이 있었다. 일부 환자들은 베이스라인에서 경증 간장애(Child-Pugh A 등급)가 동반된 대상성 간경변이 보고되었으나, 기존에 비대상성 간경변의 사례(예, 복수, 정맥류 출혈, 뇌병증)을 경험한 바 있었다. 간경변이 없거나 대상성 간경변(Child-Pugh A)을 가진 환자에서 비대상성 간경변 및 간부전이 드물게 보고되었으며, 이들 중 다수에서 문맥고혈압이 있었다. 병용이 권고되지 않는 병용 약물을 복용하는 환자 또는 심각한 간 관련 내과 또는 외과적 동반 질환과 같은 교란요인이 있는 환자에서도 사례가 보고되었다. 보고된 사례는 통상적으로 치료 시작 후 4 주 이내에 발생하였다(중간값 27일). 대상성 간경변(Child-Pugh A)이나 문맥고혈압 등 간 질환이 진행된 환자에서 임상적으로 필요한 실험실적 간 검사를 시행하고, 황달, 복수, 간성뇌병증, 정맥류 출혈과 같은 비대상성 간경변의 징후와 증상이 나타나는지 모니터링 한다. 비대상성 간경변 및 간부전으로 진행된 증거가 있는 환자는 치료를 중단한다. 중등증 또는 중증 간장애 환자(Child-Pugh B 또는 C) 또는 비대상성 간경변(hepatic decompensation) 병력이 있는 환자에게는 투여 금기이다. **2. 다음 환자에는 투여하지 말 것** 1) 이 약의 주성분 또는 구성성분에 과민증이 있는 환자 2) 중등증 또는 중증 간장애 환자(Child-Pugh B 또는 C) 또는 비대상성 간경변(hepatic decompensation) 병력이 있는 환자 3) 아타자나비르, 아토르바스타틴, 심바스타틴, 에티닐에스트라디올 함유제제, 강력한 P-gp 및 CYP3A 유도제[리팜핀, 카바마제핀, St. John's Wort(hypericum perforatum), 페니토인 등]와의 병용 4) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. **[제조원] (제조의뢰자)** AbbVie Deutschland GmbH & Co. KG, 독일, Knollstrasse 67061 Ludwigshafen (제조 및 포장) **(제조자)** Fournier Laboratories Ireland Limited, 아일랜드, Anngrove Carrigtowhill Co. Cork. **[수입원]** 한국애브비㈜, 서울특별시 강남구 영동대로 421 삼탄빌딩 6층, 전화: (02)-3429-9300 www.abbvie.co.kr **[허가변경일]** 2021년11월16일 *의약품 부작용 신고 및 피해구제 신청: 한국의약품안전관리원 (1644-6223, www.drugsafe.or.kr) *자세한 제품정보는 제품설명서를 참조해 주십시오.

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- Take once a day regardless of meal
- Less affected by CYP2C19: Low potential of DDI · individual variations

【Product name】 Fexuclue Tab. 40mg 【Formulation】 Active Pharmaceutical Ingredient: Fexuprazan HCl 40 mg Additives: lactose hydrate (bovine, milk), Yellow No.4, Microcrystalline Cellulose, Magnesium stearate, Opadry Green AMB2 88A610038, Opadry White 03B28796, Croscarmellose Sodium, Yellow Iron Oxide. 【Appearance】 Pale-green, Oblong film-coated tablet with the breaking line on the tablet 【Indication】 Treatment of erosive esophagitis (EE) 【Dosage and Administration】 The Product is administered to adults as follows. • Treatment of erosive esophagitis (EE) - 40 mg is administered orally once a day for 4 weeks. - In the case of patients with untreated esophagitis or symptoms persisting, the administration given for another 4 weeks. The Product can be administered with or without meals. 【Contraindications】 1) Patients who have a history of hypersensitivity to the Product or its components 2) Patients taking a drug containing atazanavir, nelfinavir, or rilpivirine (refer to '5. Interactions') 3) Pregnant and lactating women (refer to '6. Administration to Pregnant and Lactating Women') 4) Patients who have congenital conditions for lactose such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, as this medicine contains lactose 【The following patients should be administered with care.】 1) Patients with hepatic impairment (no experience of use) 2) Patients with renal impairment (no experience of use) 3) Elderly (refer to '8. Geriatric Use') 4) Patients who have a history of hypersensitivity or allergy to Yellow 4 Tartrazine 【Storage】 Store at temperatures not exceeding 30°C in an airtight container 【Shelf-life】 36 Months 【Availability】 28T/Box (7T/PTP*4), 56T/Box (7T/PTP*8), 28T/BtL, 100T/BtL, 300T/BtL 【Manufactured by】 Daewoong Pharmaceutical Co., Ltd./ 1, Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea ※ This medicine has passed strict quality control. If the use-by date or expiration date has passed at the time of purchase, or it the drug is spoiled, contaminated, or damaged, it can be exchanged or refunded through the pharmacy or drug distributor where it was purchased in accordance with the Fair Trade Commission Notice (Consumer Dispute Resolution Standard) ※ Report side effects and apply for damage relief: Korea Pharmaceutical Safety Management Agency (14-3330, 1644-6223)
※ For detailed and up-to-date approval information, please refer to the Ministry of Food and Drug Safety's integrated drug information system (https://nedrug.mfds.go.kr) or the product label.

GODEX® cap.

Carnitine Complex의
NAFLD 치료 효과

Beyond ALT/AST normalization effect

- ✔ Carnitine 성분의 **미토콘드리아 회복** 효과
- ✔ 영상학적으로 입증된 **지방간 개선**효과
- ✔ **인슐린 저항성 개선**효과

고덱스®캡슐

성상 | 황갈색의 분말이 들어있는 상 · 하 적갈색 불투명의 경질캡슐제 | **성분 · 함량** | 1캡슐 중 Carnitine orotate 150mg Liver extract antitoxic fraction 12.5mg Pyridoxine HCl 25mg Riboflavin 0.5mg Cyanocobalamin 0.125mg Biphenyl Dimethyl Dicarboxylate 25mg Adenine HCl 2.5mg | **효능 · 효과** | 트란스아미나제(SGPT)가 상승된 간질환 | **용법 · 용량** | 통상 성인 1회 2캡슐, 1일 2~3회 복용, 연령, 증상에 따라 적의 증감. | **사용상의 주의사항** | 1. 다음 환자는 투여 하지 말 것. 1) 이 약 및 이 약에 포함된 성분에 과민반응이 있는 환자 2) 레보도파를 투여 받고 있는 환자 2. 다음 환자는 신중히 투여할 것. 1) 만성 활동성 간염 환자 2) 간경화 환자 3. 이상반응 1) 간혹 입안마름, 메스꺼움, 발진, 가려움증, 발적 등이 생길 수 있으며, 이러한 이상반응은 투약을 중지하거나 항과민약을 병용투여하면 소실된다. 2) 일과성 황달이 나타날 수 있으나 투약을 중지하거나 황달치료제를 병용투여하면 소실된다. 3) 드물게 구역, 복부팽만, 변비, 메스꺼움, 상복부 불쾌감이 나타날 수 있다. | **보험코드** | 693900080 | **포장단위** | 100캡슐, 300캡슐(병) / 100캡슐(PTP) | **저장방법** | 기밀용기, 실온보관(1~30℃)

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B15-19 바이러스성 간염(Viral hepatitis) K70.0 알코올성 지방간(Alcoholic fatty liver) K71.0 독성 간질환(Toxic liver disease) K73.0 달리 분류되지 않은 만성 지속성 간염(Chronic persistent hepatitis, NEC) K74.0 간섬유증(Hepatic fibrosis) K75.8 기타 명시된 염증성 간질환, 비알코올성 지방간염(Other specified inflammatory liver disease, Nonalcoholic steatohepatitis) K77.0 달리 분류된 질환에서의 간장애(Liver disorders in disease classified elsewhere)

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OT2016-07

In 1L unresectable Hepatocellular Carcinoma

TECENTRIQ® + Bevacizumab (AVASTIN®) combination therapy is the first immunotherapy[1]

that demonstrated survival benefit vs. existing therapy

- Median OS : 19.2 months with TECENTRIQ® + Bevacizumab (AVASTIN®) vs 13.2 months with sorafenib (HR=0.66; 95% CI, 0.52,0.85; P<0.001*)[2]

IMBrave150 : 501patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The coprimary endpoints were OS and IRF assessed PFS.
HR : Hazard ratio **CI** : Confidence interval **OS** : Overall survival **IRF** : Independent review facility **PFS** : Progression free survival

References 1. Finn et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020:382:1894-905. May 14, 2020.
2. AL Cheng, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2021 Dec 10:S0168-8278(21)02241-8. *descriptive purpose only

M-KR-00001904

*보다 자세한 제품정보 문의 및 제품 관련 부작용 보고는 (주)한국로슈 (02-3451-3600) 로 연락 주시기 바랍니다 *가장 최신 제품정보는 ㈜한국로슈 홈페이지(www.roche.co.kr)에서 확인하실 수 있습니다

㈜한국로슈 서울특별시 서초구 서초대로 411. GT Tower(East) 빌딩 17층 (06615) Tel 02.3451.3600 / www.roche.co.kr

TECENTRIQ® atezolizumab AVASTIN® bevacizumab

For healthcare professionals only

Remarkable Response

LENVIMA® (lenvatinib) capsules
RESPONSE THAT MATTERS

The ORR was more than three times higher with lenvatinib versus control group.[1]

Based on the masked IIR according to mRECIST,

about 41% of patients* showed ≥ 30% decrease in tumor size.[1,2]

* ORR is one of the secondary endpoints and this is the result of the post-hoc exploratory tumour assessments using mRECIST by masked central independent imaging review. For more information, please refer to the full text of the article. (Kudo M, et al. 2018)

[Study design] This was an open-label, phase 3, multicentre, non-inferiority trial that recruited patients with unresectable hepatocellular carcinoma, who had not received treatment for advanced disease, at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American regions. Patients were randomly assigned (1:1) via an interactive voice-web response system with region: macroscopic portal vein invasion, extrahepatic spread, or both; Eastern Cooperative Oncology Group performance status; and bodyweight as stratification factors to receive oral lenvatinib (12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg) or sorafenib 400 mg twice-daily in 28-day cycles. The primary endpoint was overall survival, measured from the date of randomisation until the date of death from any cause. The efficacy analysis followed the intention-to-treat principle, and only patients who received treatment were included in the safety analysis. Lenvatinib(median OS 13.6 months, 95% CI 12.1-14.9) was non-inferior to sorafenib(median OS 12.3 motnhs, 95% CI 10.4-13.9) in overall survival in untreated advanced hepatocellular carcinoma(HR 0.92, 95% CI 0.79-1.06).[1]

	Lenvatinib (n=478)	Sorafetinib (n=476)	Effect size (95% CI)	*P* value
Investigator review according to mRECIST				
Objective response (%, 95% CI)	115 (24.1%, 20.2-27.9)	44 (9.2%, 6.6-11.8)	OR 3.13 (2.15-4.56)	<0.0001
Masked Independent Imaging review according to mRECIST				
Objective response (%, 95% CI)	194 (40.6%, 36.2-45.0)	59 (12.4%, 9.4-15.4)	OR 5.01 (3.59-7.01)	<0.0001
Masked Independent Imaging review according to RECIST 1.1				
Objective response (%, 95% CI)	90 (18.8%, 15.3-22.3)	31 (6.5%, 4.3-8.7)	OR 3.34 (2.17-5.14)	<0.0001

mRECIST, modified Response Evaluation Criteria in Solid Tumors; IIR, Independent imaging review; ORR, Objective Response Rate; CI, Confidence Interval; uHCC, unresectable hepatocellular carcinoma; OR, Odds ratio; OS, Overall Survival

[References] 1. Kudo M et al. Lancet. 2018 Mar 24;391(10126):1163-1173 2. Lencioni R, Llovet JM. Semin Liver Dis. 2010 Feb;30(1):52-60

Lenvim 4mg, 10mg Capsules (Lenvatinib mesilate) [Composition] 4mg capsule: Active ingredient: lenvatinib mesilate (in house specification) -4.90mg (4.0mg equivalent to lenvatinib free base) 10mg capsule: Active ingredicent: lenvatinib mesilate (in house specification) -12.25mg (10.0mg equivalent to lenvatinib free base) **[Therapeutic indication]** 1. Lenvima is indicated for the treatment of patients with progressive, locally recurrent or metastatic, differentiated thyroid carcinoma (DTC), refractory to radioactive iodine (RAI). 2. LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma. 3. LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. **[Dosage and administration]** 1) Posology **DTC** In Adults the recommended daily dose of Lenvima is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (See 2) Dose Adjustment section below). **HCC** The recommended dosage of LENVIMA is based on actual body weight: • For patients greater than or equal to 60 kg: 12 mg • For patients less than 60 kg: 8 mg Take LENVIMA orally once daily until disease progression or until unacceptable toxicity. There is no clinical evidence to support the use of 10 mg dose in HCC. **Endometrial Carcinoma** The recommended dosage of LENVIMA is 20 mg orally once daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression. Refer to the pembrolizumab prescribing information for recommended pembrolizumab dosing information. **[Precautions for Use]** 1. Contraindications 1) Hypersensitivity to the active substance or to any of the excipients 2) Breast-feeding 2. Careful Administration 1) Patients with hypertension 2) Patients with thromboembolism or a history of the condition 3) Patients with brain metastasis 4) Patients in whom the wound from a surgical procedure has not yet healed 5) Patients with tumor invasion to the cervical artery/vein, etc. **[Importer]** Eisai Korea Inc. 10F Revessant, 6, Bongeunsa-ro 86-gil, Gannam-gu, Seoul, 135-878, Korea (tel 02-3451-5500) - Date of written manual: Jul 1st, 2021 - For details, please refer to the full prescribing information.

Eisai Korea Inc.

EISAI KOREA 10F Revessant, 6, Bongeunsa-ro 86-gil, Gangnam-gu, Seoul, 06163, Korea TEL: 02-3451-5500

KR-LV-INP-200-01

GC 녹십자

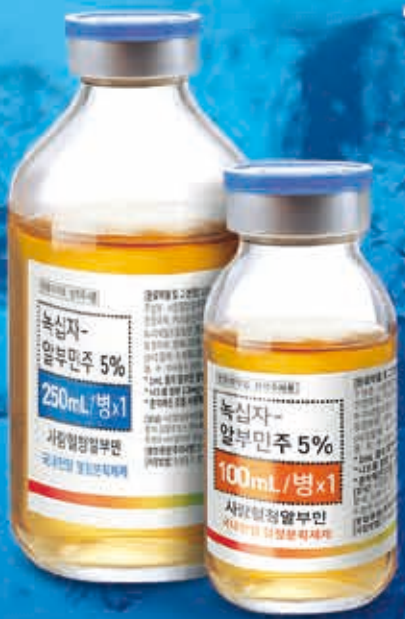
Human Serum Albumin

알부민주

- Maintenance of Plasma Colloid Osmotic Pressure
- Intravascular Volume Expansion

Indications

1. 알부민의 상실(화상, 신증후군 등)에 의한 저알부민혈증
2. 알부민 합성저하(간경변증 등)에 의한 저알부민혈증
3. 출혈성 쇽



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Experience a better tomorrow with VEMLINO

VEMILINO, Effective for early stage and impaired renal function or decreased bone mineral density of hepatitis B patients.

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Tenofovir Alafenamide Hemimalate

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- Increased affordability with lower price, 2,474/tablet[3]*
- Improved patients' compliance with daily pill bottle[4]

1. Agarwal K, et al. J Hepatol. 2018, 68, 672-681
2. Lampertico P, et al. Lancet Gastroenterol Hepatol. 2020 May;5(5):441-453.

※ The data above are clinical data conducted with Tenofovir alafenamide hemi-fumarate.

3. https://www.health.kr/searchDrug/result_drug.asp?drug_cd=2022122100010 약학정보원, 베믈리아 의약품 상세정보, accessed on April 2023
4. Vervloet M, et al. J Am Med Inform Assoc 2012;19(5):696-704

*896 won lower price than Original drug (June 2023)

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oral suspension Megace® (megestrol acetate, USP)

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식욕 개선, 체중 증가, QOL개선을 통해 암환자의 생존률 증가에 도움이 될 수 있습니다.

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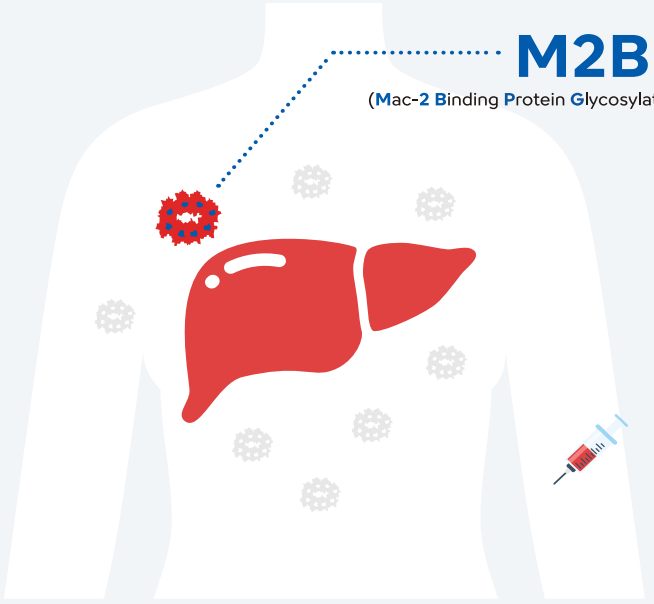
Liver Fibrosis Single Biomarker

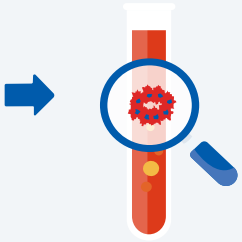


M2BPGi

(Mac-2 Binding Protein Glycosylation isomer)

[**M2BPGi** forms in blood when hepatic fibrosis occurs]

Collect blood for M2BPGi test



Measure with full **automated system**

Sysmex "HISCL-800"

The only single biomarker that is approved reimbursement (Code: D1980)

Pick up only 10㎕ of serum

Test time **17min**

Included in the KASL clinical practical guidelines for managing NAFLD and CHB

Subject & Utility of M2BPGi Test

Diabetes: There is a high possibility of advanced hepatic fibrosis with an abnormal M2BPGi level (>1.0).[1]

NAFLD patients: Serum M2BPGi could serve as a reliable biomarker for diagnosing advanced fibrosis and cirrhosis.[2]

Liver fibrosis risk population: Serum M2BPGi has proven to be a dependable, non-invasive surrogate marker for predicting advanced fibrosis.[3]

CHB patients receiving long-term antiviral treatment: The serum M2BPGi level functions as an independent predictor of HCC and complements the stratification of HCC risks.[4]

CHB with oral antiviral therapy: A baseline M2BPGi level above 1.73 consistently demonstrated predictive value for higher HCC risk.[4]

TACE treatment for HCC: The combination of M2BPGi and up-to-seven criteria could serve as a surrogate marker for predicting CP grade deterioration.[5]

CHB: The M2BPGi level can predict HCC development independently.

References

1. Park H, *et al. Ann Transl Med.* 2020;8(23):1583 **2.** Jang SY, *et al. Ann Lab Med.* 2021;41(3):302-309. **3.** Kim M, *et al. J Clin Med.* 2020;9(4):1119. **4.** Tseng TC, *et al. Liver Cancer.* 2020;9(2):207-220. **5.** Eso Y, *et al. Cancers (Basel).* 2019;11(3):405. **6.** Kim SU. *et al. Liver Int.* 2016; 1-9.

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