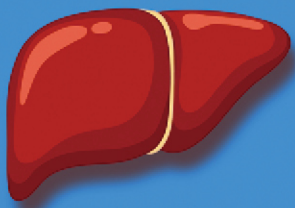
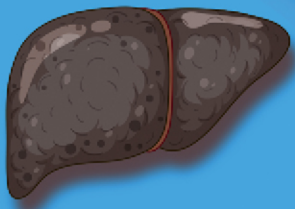
VOLUME 31 SUPPLEMENT February 2025

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases





KASL 2025 MASLD clinical practice guidelines

Prognostication of MASLD

Epidemiology of MASLD

Precision medicine and MASH

Microbiome-centered therapies for MASLD

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR
HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0837
Clinical and Molecular Hepatology 2025;31(Suppl):S182-S195

Review

Mechanisms of hepatocellular carcinoma and cirrhosis development in concurrent steatotic liver disease and chronic hepatitis B

Saisai Zhang[1], Lung-Yi Mak[1,2], Man-Fung Yuen[1,2], and Wai-Kay Seto[1,2,3]

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

Chronic hepatitis B (CHB) poses a major global public health challenge and is a leading cause of cirrhosis and liver cancer. Hepatic steatosis is common in individuals with CHB compared to the non-CHB population and is particularly prevalent in hepatitis B virus (HBV)-endemic regions, affecting about one-third of CHB patients. The interaction between hepatic steatosis and CHB-related disease progression is complex and still under debate. Evidence demonstrates that co-existing steatosis may worsen liver fibrosis while paradoxically increasing the likelihood of achieving better HBV control. In particular, despite the association of steatotic liver disease (SLD) with lower HBV viral loads and higher rates of HBsAg seroclearance, the coexistence of CHB and SLD can potentially accelerate liver disease progression. Factors such as fat deposition, lipotoxicity, oxidative stress, and chronic inflammation in SLD may foster a pro-fibrotic and pro-carcinogenic environment, accelerating the disease progression. Additionally, loss of global DNA methylation, changes in the immune microenvironment, and genetic susceptibility further contribute to the development of CHB-related cirrhosis and hepatocellular carcinoma (HCC). This review examines the mechanisms driving liver disease progression and the heightened risk of cirrhosis and HCC in patients with concurrent CHB and steatotic liver disease, underscoring the importance of prioritizing antiviral therapy for CHB in addition to addressing SLD. **(Clin Mol Hepatol 2025;31(Suppl):S182-S195)**

Keywords: Hepatitis B virus; Fatty liver; Cirrhosis; Hepatocellular carcinoma; Non-alcoholic fatty liver disease

INTRODUCTION

Chronic hepatitis B and steatotic liver disease

Chronic hepatitis B (CHB) infection is a major health burden affecting approximately 296 million people and is a prominent contributor to cirrhosis and liver cancer worldwide. Ongoing liver inflammation and fibrogenesis in CHB infection contribute to liver fibrosis and cirrhosis, with 25–40% of HBV carriers progressing to hepatocellular carcinoma (HCC).[1] The WHO 2024 global hepatitis report[2] showed a decline in incidence but an increase in mortality due to hepatitis B. In 2022, approximately 1.10 million people died due to hepatitis B. Approximately 25% of untreated CHB patients will die from complications related to cirrhosis and/or HCC, with the rate rising to 50% in men.[1] Recent Global Burden of Disease studies reported that the burden of liver cancer is predicted to rise, and it is always a threat to mor-

Corresponding author : Wai-Kay Seto
Department of Medicine, the University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong
Tel: 852 22556979, Fax: 852 28725828, E-mail: wkseto@hku.hk
https://orcid.org/0000-0002-9012-313X

Editor: Byoung Kuk Jang, Keimyung University, Korea

Received: Sep. 25, 2024 / **Revised:** Nov. 13, 2024 / **Accepted:** Nov. 16, 2024

tality both in the past and in the next 20 years.[3]

It has been reported that the prevalence of hepatic steatosis is lower in hepatitis B surface antigen (HBsAg)-positive patients than that in HBsAg-negative patients.[4] Approximately one-third of CHB patients have concurrent steatosis.[5] This co-occurrence is expected to rise due to the global increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD),[6] including in areas where CHB infection is common.[7] According to a recent meta-analysis of 98 studies with 48,472 CHB patients, the global prevalence of MASLD was about 34.93%.[8] The impact of hepatic steatosis on CHB-related disease progression remains debatable. One independent risk factor for the development of cirrhosis[9] and HCC[10] in patients with CHB is hepatic steatosis. This review explores the potential mechanisms underlying the progression to advanced liver disease, such as cirrhosis and HCC, in patients with concomitant CHB and steatotic liver disease (SLD).

STEATOSIS AND HBV ACTIVITY: AN INVERSE CORRELATION

There is no evidence that HBV infection itself directly confers excessive risk of steatosis. Nonetheless, increased hepatic steatosis was associated with reduced HBV DNA production and an increased likelihood of HBsAg seroclearance. The lower serum levels of HBV DNA, decreased hepatitis B e antigen (HBeAg) positivity and higher HBsAg seroclearance rate were observed in CHB-SLD patients. Moreover, the positivity of intrahepatic hepatitis B core antigen (HBcAg) and HBsAg was lower in treatment-naïve CHB-SLD patients.[11] A recent meta-analysis further demonstrated a negative correlation between HBV viral activity and hepatic steatosis.[5] Approximately 30% of CHB patients had hepatic steatosis, which was negatively associated with serum HBeAg and HBV DNA.[5]

The quantitative demonstration of the inverse relationship between HBV viremia and hepatic steatosis was shown in treatment-naïve CHB patients. Individuals with hepatic steatosis, quantified by controlled attenuation parameter (CAP) measurements,[12] exhibited a lower HBV viral load in a dose-dependent manner, demonstrating an independent negative correlation with hepatic steatosis and serum HBV DNA levels. Routine bedside quantification assessment of hepatic steatosis can also provide prognostic value in virologically quiescent CHB patients since fibrosis progression remains a risk for those patients with persistent severe steatosis.[13]

Mechanisms of interaction between CHB and steatosis

Mechanistic role of hepatic steatosis in CHB

There have been several studies describing potential mechanistic pathways of steatosis impacting CHB (Fig. 1). Toll-like receptor 4 (TLR4) is a vital cell surface receptor essential for initiating innate immune responses, and its specific ligand inhibits HBV replication *in vivo*.[14] Saturated fatty acids have been shown to suppress HBV replication in CHB patients with concomitant MASLD by activating the TLR4 signalling pathway.[15] Another potential pathway is via the suppression of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which can inhibit HBV replication. PGC-1α is a transcription factor crucial for gluconeogenesis, but its expression is diminished in MASLD. Consequently, the metabolic changes triggered by MASLD hinder HBV replication by downregulating PGC-1α expression.[16] Elevated levels of the death receptor-Fas on hepatocytes could trigger steatosis-induced apoptosis, potentially causing the loss of HBsAg and contributing to viral clearance.[17] Besides, reducing the level of adiponectin has been shown to inhibit HBV replication. It has been demonstrated in the *in vitro* study that adiponectin can enhance viral replication. However, the use of small interfering RNAs targeting adiponectin can prevent this enhancement,[18] as supported by a prospective study indicating a correlation between elevated adiponectin levels and in-

---

Abbreviations:

aHR, adjusted hazard ratio; CAP, controlled attenuation parameter; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; ER, endoplasmic reticulum; HBc, HBV core; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBx, HBV X; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; LPS, lipopolysaccharide; MAMPs, microbiota-associated molecular patterns; MASLD, metabolic dysfunction-associated steatotic liver disease; miRNAs, microRNAs; NTCP, sodium taurocholate cotransporting polypeptide; OBI, occult HBV infection; OR, odds ratio; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; SLD, steatotic liver disease; TLR, toll-like receptor

https://doi.org/10.3350/cmh.2024.0837

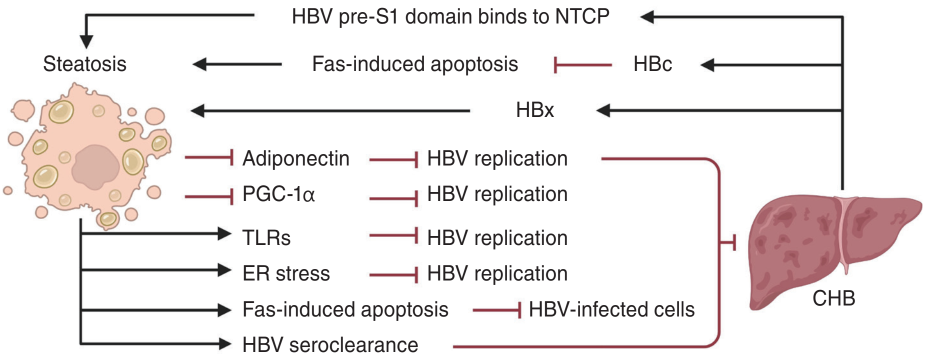


Figure 1. Mechanisms of interaction between hepatitis B and steatosis. The interaction between CHB and liver steatosis involves complex mechanisms. Liver steatosis can inhibit HBV replication through several pathways, including the induction of endoplasmic reticulum (ER) stress, activation of Toll-like receptor 4 (TLR4), and suppression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). Additionally, increased apoptosis of hepatocytes via the Fas receptor and the suppression of adiponectin, which can enhance HBV replication, contribute to reduced HBV activity in the presence of steatosis. Conversely, HBV itself can promote liver steatosis through the action of the HBx protein, which induces lipid accumulation in liver cells and also inhibits apoptosis. Additionally, HBV interferes with bile acid uptake via sodium taurocholate co-transporting polypeptide (NTCP), further contributing to steatosis. CHB, chronic hepatitis B; HBV, hepatitis B virus; HBx, HBV X; HBc, HBV core. Created with BioRender.com.

creased HBV viral load.[19] Furthermore, steatosis in hepatocytes inhibits the secretion of HBV DNA and HBsAg by activating endoplasmic reticulum (ER) stress.[20]

Mechanistic role of the HBV genome in hepatic steatosis

The presence of the HBV X (HBx) gene is a risk factor for steatosis in CHB patients and HBx overexpression leads to lipid accumulation. HBx modulates hepatic lipid metabolism by influencing the lipogenesis via traperoxisome proliferator-activated receptor gamma and sterol regulatory element-binding protein 1.[21] It has been demonstrated that HBx upregulates the expression of fatty acid-binding protein 1, leading to intrahepatic lipid accumulation and facilitating the progression of steatosis in HBV-infected cells.[22]

Other HBV genomes may also play a role in steatosis. During chronic infection, the HBV core (HBc) gene may protect infected hepatocytes from Fas-induced apoptosis via increasing antiapoptotic receptor form and decreasing the levels of the proapoptotic Fas form.[23] Moreover, the pre-S1 domain of the HBV envelope binds to sodium taurocholate co-transporting polypeptide (NTCP), the hepatic bile acid transporter,[24] reducing its ability to transport bile acid into hepatocytes, which results in elevated bile acid production, cholesterol supply, and hepatic steatosis.[25]

MECHANISMS OF MASLD-ASSOCIATED HCC AND CIRRHOSIS DEVELOPMENT

MASLD is initiated by the accumulation of fat in the liver, driven by insulin resistance, with inflammation as a critical hallmark that accelerates disease progression.[26] When fatty acid disposal through beta-oxidation or triglyceride formation is overwhelmed, excess fatty acids contribute to the formation of lipotoxic species, leading to ER stress and inflammasome activation. These mechanisms collectively result in inflammation, hepatocellular injury, stellate cell activation, and progressive accumulation of extracellular matrix, culminating in fibrosis, cirrhosis, and HCC.[27,28]

MASLD is a multifactorial disease also influenced by a combination of host genetics, epigenetics, gut microbiota, and microbial metabolites. These factors do not act independently; rather, they interact and influence one another throughout the development and progression of MASLD. Imbalance in microbial metabolites, such as branched-chain amino acids, bile acids, short-chain fatty acids, trimethylamine and endogenous ethanol, has a strong link with development of MASLD and HCC.[29-31] In addition to these metabolites, bacterial antigens such as lipopolysaccharide (LPS),[32,33] peptidoglycan,[29] flagellin,[34,35] and polysaccharide A,[36] as well as bacterial DNA in the liver have a close relationship with MASLD disease progression.[37] These factors together lead to intrahepatic lipid accumulation, persistent inflammation, and progression to MASLD-related HCC.

Due to improvements in surveillance strategies for viral hepatitis, the rising prevalence of obesity and metabolic syndrome has positioned MASLD as a dominant driver of HCC in numerous instances.[38] Although approximately half of HCC patients have MASLD, only 12% of HCC cases occur in individuals with MASLD as the sole liver disease.[39] Nevertheless, MASLD frequently serves as a cofactor in individuals with other liver disease etiologies, highlighting its broad role in the pathogenesis of HCC.

MECHANISMS OF HBV-ASSOCIATED HCC AND CIRRHOSIS DEVELOPMENT

Since HBV does not directly cause cellular damage, it is hypothesized that host immune responses targeting virus-infected hepatocytes are pivotal in liver cell damage. Prolonged liver inflammation and insufficient immune-mediated viral clearance are critical contributors to the advancement to cirrhosis and liver cancer.

Roles of HBV genome integration

One of the main causes of HBV-related HCC is the integration of the HBV genome into the genome of host hepatocytes. According to whole-genome sequencing, it was present in 80–90% of cases of HCC and in ~30% of non-HCC adjacent liver tissue, with this integration appearing before the occurrence of HCC.[40] It is worth noting that about 70% of Asian patients with HCC and occult HBV infection (OBI) have HBV DNA integration primarily affecting the HBx and preS/S domains.[41] In HCC patients with OBI, the HBV DNA integration correlates with alterations in telomerase reverse transcriptase gene activation, p53 gene mutations, tumor suppressor genes, and genomic instability.[42,43]

Roles of HBV-encoded proteins

HBsAg, HBeAg, DNA polymerase, and the HBx protein are synthesized from mRNA transcripts originating from covalently closed circular DNA (cccDNA) and/or integration into the host genome from HBV DNA. It has been documented that the IL-6-STAT3 pathway, which is activated by HBsAg, increases the malignant potential of HBV-related HCC.[44] On the other hand, HBeAg has been linked to the host's immune response and cytokine production, thereby contributing to HBV-related HCC.[45] Studies indicate that liver-specific transgenic mice expressing the reverse transcriptase domain of HBV polymerase have a tendency to develop early cirrhosis with concurrent steatosis, with approximately 10% eventually advancing to HCC.[46] Additionally, numerous studies highlighted the involvement of the HBx protein in hepatocarcinogenesis.[21,47-49] Several transcription factors can be activated by HBx, such as STAT3, NF-κβ, PI3K/AKT, leading to hepatocyte inflammation, proliferation, and apoptosis, ultimately contributing to the development of HCC.[50,51] Moreover, C-terminal truncated HBx protein plays an oncogenic role by affecting glycolysis, cell cycle, and mTORC1 signalling pathways in HCC.[52]

Roles of Inflammation

CHB triggers immune dysregulation through multiple mechanisms that contribute to HCC development.[53,54] Immune cells such as CD4+ T cells, natural killer cells, natural killer T cells, monocytes/macrophages, and hepatic stellate cells (HSCs) drive inflammation, promoting HCC progression.[55] Notably, two distinct subsets of CD8+ T cells are present in the liver: intrahepatic HBV-specific CD8+ T cells, which are associated with HBV control and viral clearance, and bystander CD8+ T cells, which are not HBV-specific but contribute to inflammation and hepatotoxicity.[56,57] On the other hand, immunosuppressive cells, including regulatory T cells, myeloid-derived suppressor cells, and Kupffer cells, potentially act as negative regulators on HCC by releasing IL-10 and TGF-β, potentially acting as negative regulators of HCC.[58,59] The persistent immune-mediated liver damage in CHB often leads to cirrhosis, which is a key precursor to HCC.

The involvement of epigenetic mechanisms

A crucial role of epigenetic mechanisms has been reported in HBV-associated HCC. MicroRNAs (miRNAs), in terms of noncoding RNAs, modulate their target genes post-transcriptionally. HBV encourages the development of HCC by activating multiple signalling pathways through various

https://doi.org/10.3350/cmh.2024.0837

miRNAs. Certain miRNAs that participate in the TLR signalling pathways play a crucial role in the innate immune response to HBV infection.[60] HBV may affect the expression of miRNAs and inflammatory cytokines. Additionally, HBV can induce changes in DNA methylation[61] as well as post-translational modifications of histones,[62] resulting in epigenetic alterations that are essential in the progression of HBV-related HCC.

Roles of gut microbiome

The gut microbiome mediates immune responses to HBV. In adult mice, the maturation of the gut microbiota stimulates liver immunity, leading to rapid HBV clearance. Conversely, when the gut microbiota is sterilized with antibiotics, this rapid clearance is prevented.[63] Patients with HBV-related HCC and non-viral HCC exhibit varying levels of bacteria associated with distinct functions or biological pathways.[64] Moreover, dysbiosis and impaired intestinal permeability cause increased hepatic exposure to and microbiota-associated molecular patterns (MAMPs). Bacterial MAMPs, such as TLR4 agonist LPS and TLR2 agonist lipoteichoic acid, stimulate hepatic HSCs activation and fibrosis, as well as macrophages, inducing inflammatory responses that promote the development of HCC.[65]

MECHANISMS OF HCC AND CIRRHOSIS DEVELOPMENT IN CONCURRENT SLD AND CHB

The increased risks of HCC and cirrhosis in SLD-CHB patients

The relationship between concurrent SLD and CHB in the development of cirrhosis and HCC is complex and not fully understood. Although both SLD and CHB are well-established risk factors for HCC, whether their co-occurrence leads to a higher risk of disease progression than CHB alone remains inconclusive. More recent studies have shown the increased risks of HCC and cirrhosis in SLD-CHB patients (Table 1). Several studies with conflicting results[66,67] possibly due to the heterogeneity of the study populations. Patients with CHB who meet the criteria for liver biopsy tend to have more severe disease, representing a minority within the broad spectrum of CHB and SLD, which may contribute to the diverse outcomes observed.[68,69]

Severe steatosis, in contrast to mild/moderate steatosis, was linked to a higher proportion of severe fibrosis in patients with CHB (23.2% and 12.6%, respectively, P=0.005).[12] A study also showed that co-existing SLD in patients with CHB leads to a higher likelihood of a functional cure from HBV but worsening liver fibrosis.[13] Severe steatosis, quantified by CAP measurements, is associated with severe fibrosis in both treatment-naïve and treated CHB patients.[70] Based on a meta-analysis that included 34 studies with a total of 68,268 CHB patients, positive associations were found between hepatic steatosis and cirrhosis (odds ratio [OR] 1.52) and HBsAg seroclearance (OR 2.22).[71] Notably, hepatic steatosis was linked to higher odds of HCC (OR 1.59), while there was no significant correlation among patients receiving nucleos(t)ide analogues (OR 1.05). Co-existing steatohepatitis with CHB leads to more advanced fibrosis and poorer liver-related outcomes or death, compared to CHB alone.[72] MASLD is an independent risk factor for developing HCC in CHB patients.[73,74] A research study utilizing data from the South Korean National Health Insurance System database discovered that, even after accounting for factors such as age, sex, antiviral treatment, alcohol consumption and cirrhosis, CHB patients with MASLD had a 1.4 times higher risk of HCC development.[75]

Furthermore, in the majority of analyses, hepatic steatosis and other systemic metabolic dysfunctions have not been distinguished, thus highlighting the combined impact of these two distinct factors on CHB patients. Different combinations of hepatic steatosis and metabolic factors are associated with varying levels of cirrhosis risk. Hepatic steatosis alone was associated with a lower risk of cirrhosis (adjusted hazard ratio [aHR] 0.57 within 5 years); however, when hepatic steatosis occurred in individuals meeting the diagnostic criteria for MASLD, the risk of cirrhosis was higher.[76] Moreover, hepatic steatosis and metabolic dysfunction had distinct impacts on HCC: steatosis protected HCC (aHR 0.45), while an increasing burden of metabolic dysfunction elevated the risk (aHR 1.40 per additional dysfunction).[77]

https://doi.org/10.3350/cmh.2024.0837

Table 1. The increased risks of disease progression in CHB patients with concurrent steatotic liver disease

Study	SLD diagnosis	Viral suppression	Disease progression	
			Cirrhosis	HCC
Aggravation				
1,202 CHB patients in a 1:1 ratio with or without steatosis[12]	VCTE	Lower median serum HBV DNA levels	Severe steatosis was associated with an increased percentage of severe fibrosis in both treatment-naïve and treated patients.	/
330 treatment-naïve patients with CHB[13]	VCTE	HBsAg seroclearance	Persistent severe hepatic steatosis was independently associated with fibrosis progression (OR 2.379).	/
606 patients with CHB[70]	VCTE	/	Severe steatosis was associated with severe fibrosis in treatment-naïve patients (OR 3.60) and treated patients (OR 1.95 for ≥3 years of treatment, 2.28 for ≥5 years of treatment, and 2.79 for ≥7 years of treatment).	/
A meta-analysis of 34 studies with 68,268 CHB patients[71]	VCTE/ biopsy-proven steatosis	HBsAg seroclearance (OR, 2.22)	Steatosis was associated with the development of cirrhosis (OR 1.52).	Hepatic steatosis was associated with higher odds of HCC (OR 1.59)
A multicenter study of 1,089 CHB patients[72]	Biopsy data	/	/	Patients with concomitant steatohepatitis and CHB had more advanced fibrosis and shorter time to develop liver-related outcomes or death compared to patients with CHB alone.
197,346 CHB participants from National Health Insurance System database in South Korea[75]	MASLD criteria	/	/	The risk of developing HCC was 1.4-fold higher in CHB patients with MASLD
11,502 CHB patients[76]	MASLD criteria	Lower HBV DNA levels	Hepatic steatosis occurred in individuals meeting the diagnostic criteria for MASLD, the risk of cirrhosis was higher	/
10,546 treatment-naïve CHB patients[77]	MASLD criteria	Fewer HBeAg positivity, lower HBV DNA levels	/	Hepatic steatosis with an increasing burden of metabolic dysfunction elevated the risk of HCC (aHR 1.40 per additional dysfunction).

HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; aHR, adjusted hazard ratio; OR, odds ratio; CT, computed tomography; HBeAg, hepatitis B e antigen; hepatitis B surface antigen; MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, steatotic liver diseases; VCTE, vibration-controlled transient elastography.

HBsAg seroclearance

Functional cure of CHB, i.e., HBsAg seroclearance, only occurs in a small percentage of patients. Nonetheless, its chances are increased with the concomitant presence of steatosis,[13,66,71,78] and may also explain why the inverse relationship between steatosis and the progression to cirrhosis and HCC was demonstrated in certain studies.[79] The exact mechanism behind the association between HBsAg seroclearance and hepatic steatosis is still unknown. One hypothesis is that the accumulation of fat in hepatocytes may alter the distribution of HBsAg within the cytoplasm, an increase in the death receptor-Fas may lead to steatosis-induced apoptosis of hepatocytes, which in turn could result in loss of HBsAg. The disruption of immune homeostasis, which is characteristic of both CHB and SLD, plays a crucial role in liver disease progression to HCC.[80] While HBV is typically not viewed as a cytopathic virus per se, hepatocellular damage can be induced by triggering immune responses within the HBV-infected hepatocytes.[17,81] The clearance of HBsAg is linked to a significant decrease in the likelihood of cirrhotic complications and HCC.[82] It remains to be investigated through further studies the extent to which the risk of such liver-related outcomes persists following HBsAg clearance in patients with hepatic steatosis. Metabolic determinants may play a role; suboptimal glycemic control has been demonstrated as a risk factor for HCC after HBsAg seroclearance.[83]

Possible mechanisms of CHB-SLD interplay leading to disease progression

Several proposed mechanisms suggest that the presence of SLD promotes CHB-related disease progression. Fat deposition, lipotoxicity, low-grade inflammatory responses and oxidative stress in SLD may create a pro-fibrotic as well as a pro-carcinogenic environment, accelerating the progression of CHB-related cirrhosis and HCC.[84-88] CHB may influence metabolic changes, contributing to the development of SLD, while HBV-induced inflammatory responses and molecular pathways could exacerbate hepatic steatosis. Interestingly, CHB has been associated with a decreased risk of hyperlipidemia and a lower prevalence of steatosis, potentially due to elevated serum adiponectin levels,[89] while HBV infection might also induce hepatic lipid accumulation via HBx overexpression and genetic susceptibility to steatosis in CHB patients.

Several underlying mechanisms are outlined (Fig. 2), even if the precise mechanisms of SLD in CHB-related disease progression are yet unknown: (1) DNA methylation: Loss of global DNA methylation, a common epigenetic modification, can lead to chromosomal abnormalities and disease progression.[90] Patients with concurrent SLD and CHB exhibit lower global DNA methylation levels compared to those with SLD alone, correlating with fibrosis and cirrhosis.[91] (2) Alterations of immune microenvironment: Immune homeostasis imbalance in CHB and SLD, characterized by disrupted immune cell function due to dysregulated

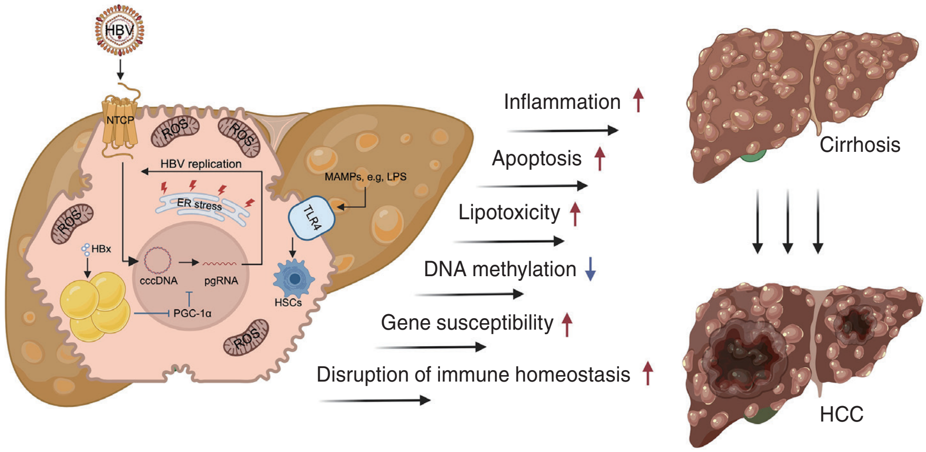


Figure 2. Potential mechanisms of interaction between steatosis and CHB in the development of cirrhosis and HCC. HBV-infected hepatocytes are believed to mediate liver cell injury and, with long-term chronic liver inflammation and ineffective immune-mediated viral clearance, lead to activation and proliferation of hepatic stellate cells. Fat deposition and oxidative stress may create a pro-fibrotic and procarcinogenic environment within the liver. In addition, abnormal lipid metabolism, gene susceptibility, and lower levels of global DNA methylation in patients with concurrent NAFLD and CHB could both accelerate the development of cirrhosis and HCC. CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NTCP, sodium taurocholate co-transporting polypeptide; ROS, reactive oxygen species; pgRNA, pregenomic RNA; cccDNA, covalently closed circular DNA; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; MAMPs, metabolites and microbiota-associated molecular patterns; LPS, lipopolysaccharide; ER, endoplasmic reticulum; TLR4, toll-like receptor 4; HCSs, hepatic stellate cells. Created with BioRender.com.

https://doi.org/10.3350/cmh.2024.0837

lipid metabolism or HBV-mediated immunosuppression, can impair anti-tumor immunity and promote liver cancer progression.[80,81,92] (3) Genetic susceptibility: Genetic factors, such as single-nucleotide polymorphisms in PNPLA3 and TM6SF2,[93,94] are associated with steatosis and inflammation in CHB patients,[95] suggesting a genetic predisposition to steatosis in this population. (4) Direct oncogenic mechanisms: Genomic instability due to HBV DNA integration into the host genome can increase oncogenic potential.[40] HBV-encoded proteins (e.g., HBx, HBc) contribute to cellular heterogeneity and tumorigenesis through various mechanisms, including stabilizing oncoproteins, inducing ER stress, and causing DNA damage.[96,97] Excessive lipid accumulation exacerbates these processes, further promoting liver cancer development.[98]

It is crucial to highlight that there are currently no robust *in vitro* or *in vivo* models specifically designed to study the interplay between steatosis and HBV. This limitation is partly due to the fact that existing HBV mouse models do not fully replicate the complete life cycle of HBV, particularly the formation of cccDNA.[99] While human liver chimeric mice and chimpanzees can exhibit a disease spectrum similar to that of humans, ethical concerns, high costs, and technical challenges associated with setting up these models make their practical application in this field unfeasible.[100] As a result, all available evidence provides only a partial understanding of the complex underlying mechanisms of the interplay between steatosis and CHB, especially regarding the pathogenesis of HCC and cirrhosis.

UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

The interplay between CHB and concurrent steatotic liver diseases presents significant challenges in managing liver disease progression. While hepatic steatosis may offer some protective effects against HBV replication, the long-term risks of cirrhosis and HCC in patients with both CHB and SLD require further investigation. Since the updated WHO guidelines[101] expand eligibility for treatment if there is the presence of MASLD, understanding the mechanisms underlying CHB and SLD interactions is crucial for developing targeted therapies and improving patient outcomes.

The potential suppression of viral activity by concurrent steatosis raises important questions. Specifically, whether simple steatosis (without other systemic metabolic dysfunction) is tolerable or even beneficial in certain populations, such as CHB patients, warrants more clinical studies. Additionally, the impact of therapeutic agents for MASLD on the disease course and prognosis of CHB remains unclear due to their exclusion from clinical trials. Future real-world studies and post-marketing clinical trial data are needed to address this gap.

Antiviral treatment with nucleos(t)ide analogues has been connected to fibrosis regression, but hepatic steatosis and metabolic syndrome are linked to fibrosis progression.[102] It has been documented[103] that the association between HBV DNA levels and HCC risk follows a nonlinear parabolic pattern, with the highest risk observed at moderate serum HBV DNA levels in treatment-naïve CHB patients. Persistent HBV DNA levels within a range of 4–8 $\log_{10}$ IU/mL in HBeAg-positive patients continue to drive clonal hepatocyte expansion, which accumulates hepatocyte damage and increases HCC risk. This risk is elevated in cases of long-term inflammation and ineffective immune clearance, contributing significantly to cirrhosis and HCC development. When immune control of HBV is achieved, HBeAg seroclearance may occur, and serum HBV DNA levels typically drop below 4 $\log_{10}$ IU/mL (inactive hepatitis phase), thus reducing HCC risk substantially. Patients who achieve HBsAg seroclearance show a time-dependent decline in liver stiffness over a decade.[104] Despite MASLD being associated with a lower HBV viral load and increased rates of HBsAg clearance, the combined effects of CHB and MASLD may synergistically accelerate liver disease progression, leading to hepatocyte injury, inflammation, fibrosis, and HCC. These findings underscore the importance of prioritizing antiviral treatment for chronic viral hepatitis before addressing MASLD.[105] Early initiation and proactive antiviral therapy may yield different outcomes for CHB patients with hepatic steatosis. A strong correlation between severe steatosis and advanced fibrosis has been reported in both treatment-naïve and treated CHB patients.[70] However, this association is less pronounced in those receiving early, potent antiviral therapy.[106] Long-term antiviral therapy, such as the use of nucleos(t)ide analogues, effectively suppresses HBV replication and slows fibrosis progression, including in patients with coexisting hepatic steatosis.[107] Further *in vitro* or *in vivo* research is essential to clarify the complex interactions between HBV and SLD in disease progression, determine the most effective therapeutic strategies, and ultimately improve long-term outcomes for affected patients.

CONCLUSION

The interplay between CHB and concurrent SLD presents a complex and evolving challenge. This review highlights the intricate balance between the potential protective effects of steatosis against HBV replication and the increased risks of cirrhosis and HCC in patients with co-existing conditions. While hepatic steatosis may be associated with lower HBV viral load and a higher rate of HBsAg seroclearance, the synergistic effects of HBV and SLD may accelerate liver disease progression, underscoring the need for careful clinical management. Current evidence suggests that antiviral therapy with nucleos(t)ide analogues is crucial for reducing fibrosis and improving liver stiffness in CHB patients. However, the role of hepatic steatosis in modifying the course of HBV-related liver disease, particularly in terms of fibrosis progression and cancer risk, requires further investigation. The potential impact of emerging treatments for MASLD on HBV-related outcomes is another area that warrants more focused research.

Authors' contributions

S Zhang: Conceptualization, literature review, writing and original draft preparation; LY Mak: Review, critical revision; MF Yuen: Review, critical revision, final approval of published version; WK Seto: Review, critical revision, final approval of published version.

Conflicts of Interest

MF Yuen is an advisory board member and/or received research funding from AbbVie, Arbutus Biopharma, Assembly Biosciences, Bristol Myer Squibb, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals; and received research funding from Arrowhead Pharmaceuticals, Fujirebio Incorporation and Sysmex Corporation. WK Seto received speaker's fees from AstraZeneca and Mylan, is an advisory board member of CSL Behring, is an advisory board member and received speaker's fees from AbbVie, and is an advisory board member, received speaker's fees and research fund from Gilead Sciences. The remaining authors have no conflicts to disclose.

REFERENCES

1. Yuen MF, Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, et al. Hepatitis B virus infection. Nat Rev Dis Primers 2018;4:18035.
2. World Health Organization (WHO). Global Hepatitis Report, 2024. Geneva: WHO, 2024.
3. Oh JH, Jun DW. The latest global burden of liver cancer: a past and present threat. Clin Mol Hepatol 2023;29:355-357.
4. Joo EJ, Chang Y, Yeom JS, Ryu S. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study. Hepatology 2017;65:828-835.
5. Zheng Q, Zou B, Wu Y, Yeo Y, Wu H, Stave CD, et al. Systematic review with meta-analysis: prevalence of hepatic steatosis, fibrosis and associated factors in chronic hepatitis B. Aliment Pharmacol Ther 2021;54:1100-1109.
6. Le MH, Yeo YH, Li X, Li J, Zou B, Wu Y, et al. 2019 Global NAFLD prevalence: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2022;20:2809-2817.e28.
7. Wong MCS, Huang JLW, George J, Huang J, Leung C, Eslam M, et al. The changing epidemiology of liver diseases in the Asia-Pacific region. Nat Rev Gastroenterol Hepatol 2019;16:57-73.
8. Jiang D, Chen C, Liu X, Huang C, Yan D, Zhang X, et al. Concurrence and impact of hepatic steatosis on chronic hepatitis B patients: a systematic review and meta-analysis. Ann Transl Med 2021;9:1718.
9. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. J Hepatol 2017;67:862-873.
10. Chan AW, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, et al. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. J Gastroenterol Hepatol 2017;32:667-676.
11. Wang MM, Wang GS, Shen F, Chen GY, Pan Q, Fan JG. Hepatic steatosis is highly prevalent in hepatitis B patients and negatively associated with virological factors. Dig Dis Sci 2014;59:2571-2579.
12. Hui RWH, Seto WK, Cheung KS, Mak LY, Liu KSH, Fung J, et al. Inverse relationship between hepatic steatosis and hepa-

https://doi.org/10.3350/cmh.2024.0837

titis B viremia: results of a large case-control study. J Viral Hepat 2018;25:97-104.

13. Mak LY, Hui RW, Fung J, Liu F, Wong DK, Cheung KS, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. J Hepatol 2020;73:800-806.
14. Isogawa M, Robek MD, Furuichi Y, Chisari FV. Toll-like receptor signaling inhibits hepatitis B virus replication in vivo. J Virol 2005;79:7269-7272.
15. Zhang RN, Pan Q, Zhang Z, Cao HX, Shen F, Fan JG. Saturated fatty acid inhibits viral replication in chronic hepatitis B virus infection with nonalcoholic fatty liver disease by toll-like receptor 4-mediated innate immune response. Hepat Mon 2015;15:e27909.
16. Piccinin E, Villani G, Moschetta A. Metabolic aspects in NAFLD, NASH and hepatocellular carcinoma: the role of PGC1 coactivators. Nat Rev Gastroenterol Hepatol 2019;16: 160-174.
17. Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, et al. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology 2003;125:437-443.
18. Yoon S, Jung J, Kim T, Park S, Chwae YJ, Shin HJ, et al. Adiponectin, a downstream target gene of peroxisome proliferator-activated receptor γ, controls hepatitis B virus replication. Virology 2011;409:290-298.
19. Wong VW, Wong GL, Yu J, Choi PC, Chan AW, Chan HY,et al. Interaction of adipokines and hepatitis B virus on histological liver injury in the Chinese. Am J Gastroenterol 2010;105:132-138.
20. Liu Q, Mu M, Chen H, Zhang G, Yang Y, Chu J, et al. Hepatocyte steatosis inhibits hepatitis B virus secretion via induction of endoplasmic reticulum stress. Mol Cell Biochem 2022;477:2481-2491.
21. Kim KH, Shin HJ, Kim K, Choi HM, Rhee SH, Moon HB, et al. Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARgamma. Gastroenterology 2007;132:1955-1967.
22. Wu YL, Peng XE, Zhu YB, Yan XL, Chen WN, Lin X. Hepatitis B virus x protein induces hepatic steatosis by enhancing the expression of liver fatty acid binding protein. J Virol 2016;90:1729-1740.
23. Liu W, Lin YT, Yan XL, Ding YL, Wu YL, Chen WN, et al. Hepatitis B virus core protein inhibits Fas-mediated apoptosis of hepatoma cells via regulation of mFas/FasL and sFas expression. FASEB J 2015;29:1113-1123.
24. Yan H, Zhong G, Xu G, He W, Jing Z, Gao Z, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife 2012;1:e00049.
25. Oehler N, Volz T, Bhadra OD, Kah J, Allweiss L, Giersch K, et al. Binding of hepatitis B virus to its cellular receptor alters the expression profile of genes of bile acid metabolism. Hepatology 2014;60:1483-1493.
26. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24:908-922.
27. Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. Nat Rev Gastroenterol Hepatol 2023;20:633-646.
28. Ma Y, Wang J, Xiao W, Fan X. A review of MASLD-related hepatocellular carcinoma: progress in pathogenesis, early detection, and therapeutic interventions. Front Med (Lausanne) 2024;11:1410668.
29. Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol 2020;17:279-297.
30. Wei W, Wong CC, Jia Z, Liu W, Liu C, Ji F, et al. Parabacteroides distasonis uses dietary inulin to suppress NASH via its metabolite pentadecanoic acid. Nat Microbiol 2023;8:1534-1548.
31. Lau HC, Zhang X, Ji F, Lin Y, Liang W, Li Q, et al. Lactobacillus acidophilus suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma through producing valeric acid. EBioMedicine 2024;100:104952.
32. Dapito DH, Mencin A, Gwak GY, Pradere JP, Jang MK, Mederacke I, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell 2012;21:504-516.
33. Jin M, Lai Y, Zhao P, Shen Q, Su W, Yin Y, et al. Effects of peptidoglycan on the development of steatohepatitis. Biochim Biophys Acta Mol Cell Biol Lipids 2020;1865:158595.
34. Shen B, Gu T, Shen Z, Zhou C, Guo Y, Wang J, et al. Escherichia coli promotes endothelial to mesenchymal transformation of liver sinusoidal endothelial cells and exacerbates nonalcoholic fatty liver disease via its flagellin. Cell Mol Gastroenterol Hepatol 2023;16:857-879.
35. Xiao Y, Liu F, Yang J, Zhong M, Zhang E, Li Y, et al. Overactivation of TLR5 signaling by high-dose flagellin induces liver injury in mice. Cell Mol Immunol 2015;12:729-742.
36. Shen Y, Giardino Torchia ML, Lawson GW, Karp CL, Ashwell

JD, Mazmanian SK. Outer membrane vesicles of a human commensal mediate immune regulation and disease protection. Cell Host Microbe 2012;12:509-520.

37. Sookoian S, Salatino A, Castaño GO, Landa MS, Fijalkowky C, Garaycoechea M, et al. Intrahepatic bacterial metataxonomic signature in non-alcoholic fatty liver disease. Gut 2020;69:1483-1491.
38. van der Spek DPC, Katwaroe WK, van Kleef LA, Brakenhoff S, de Man RA, de Knegt RJ, et al. Time-trends in disease characteristics and comorbidities in patients with chronic hepatitis B in the period 1980-2020. Eur J Intern Med 2023;107:86-92.
39. Crane H, Eslick GD, Gofton C, Shaikh A, Cholankeril G, Cheah M, et al. Global prevalence of metabolic dysfunction-associated fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Clin Mol Hepatol 2024;30:436-448.
40. Sung WK, Zheng H, Li S, Chen R, Liu X, Li Y, et al. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. Nat Genet 2012;44:765-769.
41. Wong DK, Cheng SCY, Mak LL, To EW, Lo RC, Cheung TT, et al. Among patients with undetectable hepatitis B surface antigen and hepatocellular carcinoma, a high proportion has integration of HBV DNA into hepatocyte DNA and no cirrhosis. Clin Gastroenterol Hepatol 2020;18:449-456.
42. Mak LY, Wong DK, Pollicino T, Raimondo G, Hollinger FB, Yuen MF. Occult hepatitis B infection and hepatocellular carcinoma: Epidemiology, virology, hepatocarcinogenesis and clinical significance. J Hepatol 2020;73:952-964.
43. Sze KM, Ho DW, Chiu YT, Tsui YM, Chan LK, Lee JM, et al. Hepatitis B virus-telomerase reverse transcriptase promoter integration harnesses host ELF4, resulting in telomerase reverse transcriptase gene transcription in hepatocellular carcinoma. Hepatology 2021;73:23-40.
44. Hadziyannis E, Laras A. Viral Biomarkers in chronic HBeAg negative HBV infection. Genes (Basel) 2018;9:469.
45. Song J, Zhang X, Ge Q, Yuan C, Chu L, Liang HF, et al. CRISPR/Cas9-mediated knockout of HBsAg inhibits proliferation and tumorigenicity of HBV-positive hepatocellular carcinoma cells. J Cell Biochem 2018;119:8419-8431.
46. Chung HJ, Chen X, Yu Y, Lee HK, Song CH, Choe H, et al. A critical role of hepatitis B virus polymerase in cirrhosis, hepatocellular carcinoma, and steatosis. FEBS Open Bio 2018;8:130-145.
47. Kekulé AS, Lauer U, Weiss L, Luber B, Hofschneider PH. Hepatitis B virus transactivator HBx uses a tumour promoter signalling pathway. Nature 1993;361:742-745.
48. Keng VW, Tschida BR, Bell JB, Largaespada DA. Modeling hepatitis B virus X-induced hepatocellular carcinoma in mice with the Sleeping Beauty transposon system. Hepatology 2011;53:781-790.
49. Wang C, Yang W, Yan HX, Luo T, Zhang J, Tang L, et al. Hepatitis B virus X (HBx) induces tumorigenicity of hepatic progenitor cells in 3,5-diethoxycarbonyl-1,4-dihydrocollidine-treated HBx transgenic mice. Hepatology 2012;55:108-120.
50. Cho HK, Kim SY, Yoo SK, Choi YH, Cheong J. Fatty acids increase hepatitis B virus X protein stabilization and HBx-induced inflammatory gene expression. FEBS J 2014;281:2228-2239.
51. Sivasudhan E, Blake N, Lu Z, Meng J, Rong R. Hepatitis B viral protein HBx and the molecular mechanisms modulating the hallmarks of hepatocellular carcinoma: a comprehensive review. Cells 2022;11:741.
52. Zhang Y, Yan Q, Gong L, Xu H, Liu B, Fang X, et al. C-terminal truncated HBx initiates hepatocarcinogenesis by downregulating TXNIP and reprogramming glucose metabolism. Oncogene 2021;40:1147-1161.
53. Kennedy PTF, Litwin S, Dolman GE, Bertoletti A, Mason WS. Immune tolerant chronic hepatitis B: the unrecognized risks. Viruses 2017;9:96.
54. Wu S, Kanda T, Nakamoto S, Jiang X, Nakamura M, Sasaki R, et al. Cooperative effects of hepatitis B virus and TNF may play important roles in the activation of metabolic pathways through the activation of NF-κB. Int J Mol Med 2016;38:475-481.
55. Li X, Su Y, Hua X, Xie C, Liu J, Huang Y, et al. Levels of hepatic Th17 cells and regulatory T cells upregulated by hepatic stellate cells in advanced HBV-related liver fibrosis. J Transl Med 2017;15:75.
56. Nkongolo S, Mahamed D, Kuipery A, Sanchez Vasquez JD, Kim SC, Mehrotra A, et al. Longitudinal liver sampling in patients with chronic hepatitis B starting antiviral therapy reveals hepatotoxic CD8+ T cells. J Clin Invest 2023;133:e158903.
57. Luxenburger H, Neumann-Haefelin C. Liver-resident CD8+ T cells in viral hepatitis: not always good guys. J Clin Invest 2023;133:e165033.
58. Cho HJ, Cheong JY. Role of immune cells in patients with hepatitis B virus-related hepatocellular carcinoma. Int J Mol Sci 2021;22:8011.
59. Xu L, Yin W, Sun R, Wei H, Tian Z. Kupffer cell-derived IL-10 plays a key role in maintaining humoral immune tolerance in

https://doi.org/10.3350/cmh.2024.0837

hepatitis B virus-persistent mice. Hepatology 2014;59:443-452.

60. Jiang X, Kanda T, Wu S, Nakamura M, Miyamura T, Nakamoto S, et al. Regulation of microRNA by hepatitis B virus infection and their possible association with control of innate immunity. World J Gastroenterol 2014;20:7197-206.
61. Zhao J, Wu G, Bu F, Lu B, Liang A, Cao L, et al. Epigenetic silence of ankyrin-repeat-containing, SH3-domain-containing, and proline-rich-region- containing protein 1 (ASPP1) and ASPP2 genes promotes tumor growth in hepatitis B virus-positive hepatocellular carcinoma. Hepatology 2010;51:142-153.
62. Salerno D, Chiodo L, Alfano V, Floriot O, Cottone G, Paturel A, et al. Hepatitis B protein HBx binds the DLEU2 lncRNA to sustain cccDNA and host cancer-related gene transcription. Gut 2020;69:2016-2024.
63. Chou HH, Chien WH, Wu LL, Cheng CH, Chung CH, Horng JH, et al. Age-related immune clearance of hepatitis B virus infection requires the establishment of gut microbiota. Proc Natl Acad Sci U S A 2015;112:2175-2180.
64. Liu Q, Li F, Zhuang Y, Xu J, Wang J, Mao X, et al. Alteration in gut microbiota associated with hepatitis B and non-hepatitis virus related hepatocellular carcinoma. Gut Pathog 2019;11:1.
65. Schwabe RF, Greten TF. Gut microbiome in HCC - mechanisms, diagnosis and therapy. J Hepatol 2020;72:230-238.
66. Li J, Yang HI, Yeh ML, Le MH, Le AK, Yeo YH, et al. Association between fatty liver and cirrhosis, hepatocellular carcinoma, and hepatitis B surface antigen seroclearance in chronic hepatitis B. J Infect Dis 2021;224:294-302.
67. Mak LY, Hui RW, Fung J, Liu F, Wong DK, Li B, et al. Reduced hepatic steatosis is associated with higher risk of hepatocellular carcinoma in chronic hepatitis B infection. Hepatol Int 2021;15:901-911.
68. Le MH, Le DM, Baez TC, Dang H, Nguyen VH, Lee K, et al. Global incidence of adverse clinical events in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Clin Mol Hepatol 2024;30:235-246.
69. Mak LY. Steatotic liver disease: know your enemies. Clin Mol Hepatol 2024;30:171-173.
70. Seto WK, Hui RWH, Mak LY, Fung J, Cheung KS, Liu KSH, et al. Association between hepatic steatosis, measured by controlled attenuation parameter, and fibrosis burden in chronic hepatitis B. Clin Gastroenterol Hepatol 2018;16:575-583.e2.
71. Mao X, Cheung KS, Peng C, Mak LY, Cheng HM, Fung J, et al. Steatosis, HBV-related HCC, cirrhosis, and HBsAg seroclearance: a systematic review and meta-analysis. Hepatology 2023;77:1735-1745.
72. Choi HSJ, Brouwer WP, Zanjir WMR, de Man RA, Feld JJ, Hansen BE, et al. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. Hepatology 2020;71:539-548.
73. Lin M, Gao B, Peng M, Chen X, Xiao H, Shi M, et al. Metabolic dysfunction-associated steatotic liver disease increases hepatocellular carcinoma risk in chronic hepatitis B patients: a retrospective cohort study. Front Physiol 2024;15:1347459.
74. van Kleef LA, Choi HSJ, Brouwer WP, Hansen BE, Patel K, de Man RA, et al. Metabolic dysfunction-associated fatty liver disease increases risk of adverse outcomes in patients with chronic hepatitis B. JHEP Rep 2021;3:100350.
75. Yun B, Ahn SH, Oh J, Yoon JH, Kim BK. Effect of metabolic dysfunction-associated fatty liver disease on liver cancer risk in a population with chronic hepatitis B virus infection: a nationwide study. Hepatol Res 2022;52:975-984.
76. Huang SC, Su TH, Tseng TC, Liao SH, Hsu SJ, Hong CM, et al. Pre-existing and new-onset metabolic dysfunctions increase cirrhosis and its complication risks in chronic hepatitis B. Am J Gastroenterol 2025;120:401-409.
77. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liao SH, et al. Distinct effects of hepatic steatosis and metabolic dysfunction on the risk of hepatocellular carcinoma in chronic hepatitis B. Hepatol Int 2023;17:1139-1149.
78. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liu CH, et al. Metabolic dysfunction-associated steatotic liver disease facilitates hepatitis B surface antigen seroclearance and seroconversion. Clin Gastroenterol Hepatol 2024;22:581-590.e6.
79. Yuen MF, Wong DK, Fung J, Ip P, But D, Hung I, et al. HBsAg seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology 2008;135:1192-1199.
80. Ali A, Abdel-Hafiz H, Suhail M, Al-Mars A, Zakaria MK, Fatima K, et al. Hepatitis B virus, HBx mutants and their role in hepatocellular carcinoma. World J Gastroenterol 2014;20:10238-10248.
81. Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. Nat Rev Immunol 2022;22:19-32.
82. Yip TC, Wong GL, Chan HL, Tse YK, Lam KL, Lui GC, et al. HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide

analogues. J Hepatol 2019;70:361-370.
83. Cheuk-Fung Yip T, Wai-Sun Wong V, Lik-Yuen Chan H, Tse YK, Pik-Shan Kong A, Long-Yan Lam K, et al. Effects of diabetes and glycemic control on risk of hepatocellular carcinoma after seroclearance of hepatitis B surface antigen. Clin Gastroenterol Hepatol 2018;16:765-773.e2.
84. Lebeaupin C, Vallée D, Hazari Y, Hetz C, Chevet E, Bailly-Maitre B. Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease. J Hepatol 2018;69:927-947.
85. Hirsova P, Gores GJ. Death receptor-mediated cell death and proinflammatory signaling in nonalcoholic steatohepatitis. Cell Mol Gastroenterol Hepatol 2015;1:17-27.
86. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol 2019;19:477-489.
87. Tong X, Song Y, Yin S, Wang J, Huang R, Wu C, et al. Clinical impact and mechanisms of hepatitis B virus infection concurrent with non-alcoholic fatty liver disease. Chin Med J (Engl) 2022;135:1653-1663.
88. Ma C, Kesarwala AH, Eggert T, Medina-Echeverz J, Kleiner DE, Jin P, et al. NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. Nature 2016;531:253-257.
89. Huang SC, Liu CJ. Chronic hepatitis B with concurrent metabolic dysfunction-associated fatty liver disease: challenges and perspectives. Clin Mol Hepatol 2023;29:320-331.
90. Eden A, Gaudet F, Waghmare A, Jaenisch R. Chromosomal instability and tumors promoted by DNA hypomethylation. Science 2003;300:455.
91. Li F, Ou Q, Lai Z, Pu L, Chen X, Wang L, et al. The co-occurrence of chronic hepatitis B and fibrosis is associated with a decrease in hepatic global DNA methylation levels in patients with non-alcoholic fatty liver disease. Front Genet 2021;12:671552.
92. Lim CJ, Lee YH, Pan L, Lai L, Chua C, Wasser M, et al. Multidimensional analyses reveal distinct immune microenvironment in hepatitis B virus-related hepatocellular carcinoma. Gut 2019;68:916-927.
93. Krawczyk M, Rau M, Schattenberg JM, Bantel H, Pathil A, Demir M, et al. Combined effects of the PNPLA3 rs738409, TM6SF2 rs58542926, and MBOAT7 rs641738 variants on NAFLD severity: a multicenter biopsy-based study. J Lipid Res 2017;58:247-255.
94. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: clinical impact. J Hepatol 2018;68:268-279.
95. Eslam M, Mangia A, Berg T, Chan HL, Irving WL, Dore GJ, et al. Diverse impacts of the rs58542926 E167K variant in TM6SF2 on viral and metabolic liver disease phenotypes. Hepatology 2016;64:34-46.
96. Zhao LH, Liu X, Yan HX, Li WY, Zeng X, Yang Y, et al. Genomic and oncogenic preference of HBV integration in hepatocellular carcinoma. Nat Commun 2016;7:12992.
97. Liu W, Guo TF, Jing ZT, Yang Z, Liu L, Yang YP, et al. Hepatitis B virus core protein promotes hepatocarcinogenesis by enhancing Src expression and activating the Src/PI3K/Akt pathway. FASEB J 2018;32:3033-3046.
98. Rizzo GEM, Cabibbo G, Craxì A. Hepatitis B virus-associated hepatocellular carcinoma. Viruses 2022;14:986.
99. Allweiss L, Dandri M. Experimental in vitro and in vivo models for the study of human hepatitis B virus infection. J Hepatol 2016;64(1 Suppl):S17-S31.
100. Zhang J, Lin S, Jiang D, Li M, Chen Y, Li J, et al. Chronic hepatitis B and non-alcoholic fatty liver disease: Conspirators or competitors? Liver Int 2020;40:496-508.
101. Easterbrook PJ, Luhmann N, Bajis S, Min MS, Newman M, Lesi O, et al. WHO 2024 hepatitis B guidelines: an opportunity to transform care. Lancet Gastroenterol Hepatol 2024;9:493-495.
102. Cho H, Lee YB, Ha Y, Chon YE, Kim MN, Lee JH, et al. Changes in liver stiffness values assessed using transient elastography in chronic hepatitis B patients treated with tenofovir disoproxil fumarate: a prospective observational study. BMC Gastroenterol 2023;23:210.
103. Kim GA, Han S, Choi GH, Choi J, Lim YS. Moderate levels of serum hepatitis B virus DNA are associated with the highest risk of hepatocellular carcinoma in chronic hepatitis B patients. Aliment Pharmacol Ther 2020;51:1169-1179.
104. Mak LY, Seto WK, Hui RW, Fung J, Wong DK, Lai CL, et al. Fibrosis evolution in chronic hepatitis B e antigen-negative patients across a 10-year interval. J Viral Hepat 2019;26:818-827.
105. Lee MH, Chen YT, Huang YH, Lu SN, Yang TH, Huang JF, et al. Chronic viral hepatitis B and C outweigh MASLD in the associated risk of cirrhosis and HCC. Clin Gastroenterol Hepatol 2024;22:1275-1285.e2.
106. Kim DS, Jeon MY, Lee HW, Kim BK, Park JY, Kim DY, et al. Influence of hepatic steatosis on the outcomes of patients with chronic hepatitis B treated with entecavir and tenofovir.

Clin Mol Hepatol 2019;25:283-293.

107. Hu D, Wang P, Wang X, Hu X, Huang D, Yan W, et al. The efficacy of antiviral treatment in chronic hepatitis B patients with hepatic steatosis. Heliyon 2024;10:e28653