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Review

Coexistent Hepatitis B Virus and Metabolic Dysfunction-Associated Steatotic Liver Disease Under the New Definition: A New Era for Established Diseases

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Abstract

Dysfunction-associated steatotic liver disease (MASLD) is a newly introduced term for the condition previously known as nonalcoholic fatty liver disease (NAFLD). MASLD affects 38% of the global population and is now diagnosed based on the presence of steatosis but also with cardiometabolic risk factors indicating metabolic dysfunction. Chronic hepatitis B (CHB), another significant public health issue, impacts over 296 million people worldwide, or approximately 3.2% of the global population. Studies have consistently reported a complex relationship between MASLD and CHB. Previous studies indicate that MASLD may protect against high viral loads, while other studies indicate that coexisting MASLD and CHB may lead to more advanced fibrosis and an elevated risk of HCC. Additionally, numerous studies highlight a strong association between CHB and metabolic syndrome components. This review article examines the relationship between CHB and MASLD, considering what has been previously published.

Keywords: chronic hepatitis B; metabolic dysfunction-associated steatotic liver disease (MASLD); hepatocellular carcinoma (HCC); liver fibrosis; antiviral therapy

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver condition characterized by hepatic steatosis in the absence of significant alcohol intake and other causes of chronic liver disease [1]. In 2020, a new nomenclature has been proposed, metabolic dysfunction-associated fatty liver disease (MAFLD), to replace NAFLD, aiming for criteria that emphasize positive diagnostic indicators rather than the exclusionary approach of NAFLD [2]. However, hepatology associations raised concerns regarding MAFLD, criticizing the removal of alcohol consumption limits in the criteria, the potentially stigmatizing term "fatty," and the overlap etiology of various liver diseases. As an alternative, they introduced the term metabolic dysfunction-associated steatotic liver disease (MASLD) with revised diagnostic criteria [3]. These criteria require hepatic steatosis without other identifiable causes, alongside cardiometabolic risk factors (CMRF) and specified limits on alcohol intake. Alcohol consumption beyond these limits leads to a classification of alcoholic liver disease or MetALD. Individuals with MASLD and accompanying steatohepatitis are classified as

Check for updates

Academic Editor: Melanie Deutsch

Received: 5 February 2026
Revised: 13 April 2026
Accepted: 13 May 2026
Published: 21 May 2026

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having metabolic dysfunction-associated steatohepatitis (MASH), while those with hepatic steatosis but no CMRF or other liver disease causes are defined as having cryptogenic SLD.

The current global prevalence of MASLD is approximately 38%, with even higher rates reported in regions such as the Middle East, where nearly half of the population may be affected [4].

Hepatitis B virus is among the most prevalent hepatotropic viruses, causing chronic hepatitis B (CHB) in over 296 million people globally. This accounts for approximately 3.2% of the world's population, suggesting an overlap between CHB and MASLD [5]. Studies [6,7] indicate that about 29.6% of patients with CHB also have MASLD. The effect of MASLD on CHB has been widely explored; some research suggests that hepatic steatosis may increase the likelihood of seroconversion of hepatitis B surface antigen (HBsAg) [8], while others' findings associate steatosis with poorer outcomes in CHB patients [9]. Additionally, CHB has been linked to changes in metabolic pathways, leading to increased synthesis of free fatty acids (FFA) and consequently a higher incidence of MASLD [10].

Previous findings indicate a strong association between CHB and hepatic steatosis, as described under the former term NAFLD. However, the recent shift to the term MASLD calls for a reassessment of how this new classification may influence the relationship between MASLD and CHB, particularly regarding metabolism, immunity, genetics, and the effects of treatments on both conditions. This review examines the relationship between CHB and MASLD, especially following the renaming of the disease, and considers how this might impact management strategies for CHB (Table 1).

Table 1. Studies that discussed the coexistence of CHB and the new terms of hepatic steatosis.

Study	Nomenclature	Total Cohort Number	Subgroup (MASLD/MAFLD) or CHB	Patients	Conclusion
Huang et al. 2024 [11]	MASLD	4084	887	CHB treatment-naive	MASLD patients had lower HBsAg and viral load and a higher chance of HBsAg clearance
Lee et al. 2024 [12]	MASLD	122,669 (MASLD)	16,859 (CHB)	CHB	MASLD increased the risk of cirrhosis and HCC in patients with CHB
Huang et al. 2024 [13]	MASLD	11,502	7314 (metabolic dysfunction)	CHB treatment naïve noncirrhotic	Patients with MASLD exhibited a higher cirrhosis risk and lower viral load
Han et al. 2024 [14]	MASLD	155	38	CHB-HCC received ICI	MASLD resulted in poorer efficacy of ICI and shorter PFS
Hong et al. 2024 [15]	MASLD	1818	974	CHB with MASLD	Those with MASLD and those with >2 CMRF had higher fibrosis stage
Huynh et al. 2024 [16]	MASLD	952	275	CHB-HCC underwent curative resection	MASLD improved survival in patients with CHB-related HCC following curative resection, especially in females with BMI $\geq$ 23 and noncirrhotic patients
Rui et al. 2024 [17]	MASLD	1063	--	CHB with MASLD	Lower diagnostic accuracy of noninvasive tests for fibrosis in patients with MASLD and CHB and those with >1CMRF
Lin et al. 2024 [18]	MASLD	1613	483	CHB with liver biopsy	MASLD increased the risk of HCC

Table 1. *Cont.*

Study	Nomenclature	Total Cohort Number	Subgroup (MASLD/MAFLD) or CHB	Patients	Conclusion
Adali et al. 2024 [19]	MASLD	535	187	CHB on antivirals	CMRF increased the risk of HCC
Wu et al. 2024 [20]	MAFLD	382	272	CHB with liver biopsy	Patients with MAFLD have an increased risk of advanced fibrosis. MAFLD with type 2 diabetes mellitus was associated with advanced fibrosis.
Yi et al. 2024 [21]	MAFLD	272	144	CHB treatment-naïve or stopped antiviral treatment for >6 months	The viral load and HbsAg were lower in patients with MASLD
Rugivarodom et al. 2023 [22]	MAFLD	868	152	CHB with liver biopsy	MAFLD increased the risk of long-term mortality transplantation adverse events in patients with CHB
Lv et al. 2023 [23]	MAFLD	401 (MAFLD)	179 (CHB)	CHB with liver biopsy	MAFLD and CMRF increased the risk of fibrosis MAFLD requires noninvasive exclusion of fibrosis, and if advanced fibrosis, then a liver biopsy
Chen et al. 2022 [24]	MAFLD	399	112	Treatment-naïve CHB with liver biopsy	Increased risk of liver fibrosis and hepatitis in HBeAg-negative CHB patients
Xue et al. 2022 [25]	MAFLD	549	169	HBV-related HCC	MAFLD increased the risk of poor prognosis, especially if ≥2 CMRF
Wang et al. 2022 [26]	MAFLD	1223	355	CHB patients	MAFLD increased the risk of cirrhosis
Van Kleef et al. 2021 [27]	MAFLD	1076	279	CHB with liver biopsy	MAFLD increased the risk of liver-related adverse events and death

BMI, body mass index; CHB, chronic hepatitis B; CMRF, cardiometabolic risk factor; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; PFS, progression-free survival.

2. Search Strategy

A thorough search of electronic databases such as PubMed, Web of Science, and Google Scholar was performed to find relevant published literature. The search included keywords and MeSH terms like "Chronic Hepatitis B," "CHB," "MASLD," "MAFLD," "NAFLD," "steatosis," and "antiviral therapy."

3. Coexistence of MASLD and CHB

Despite evidence of overlap between the two diseases, with up to one-third (29.9%) of CHB patients also diagnosed with MASLD, multiple studies have reported a lower prevalence of hepatic steatosis among CHB patients compared to the general population [28,29]. In a large cohort of CHB patients, Joo et al. observed a lower incidence of MASLD in individuals with CHB than in those without it [30]. Additionally, a study found that intrahepatic levels of HBsAg were inversely associated with hepatic steatosis, as confirmed by liver biopsy, and identified as an independent factor that may prevent hepatic steatosis [31].

These findings suggest that CHB impacts lipid metabolism in the liver by disrupting normal lipid processing. Since hepatic steatosis is positively correlated with elevated

triglyceride levels, CHB is associated with lower lipid profile values [32]. Researchers have explored the mechanisms behind this inverse relationship in basic studies. Findings indicate that adiponectin (a hormone secreted by adipose tissue that inhibits hepatic steatosis and enhances insulin sensitivity [33]) was found to be elevated in CHB patients with high viral loads [34].

4. The Interaction Between MASLD and CHB

In MASLD, innate immunity activation enhances the antiviral response against CHB. Additionally, metabolic dysregulation contributes to a decline in DNA replication. Increased apoptosis and decreased autophagy lead to a decrease in viral host cell survival. Furthermore, genetic alterations influence CHB replication. In case of CHB, the binding of PreS1 to the basolateral membrane receptor NTCP decreases its physiological activity, impairing bile salt transport and leading to elevated cholesterol levels. HBx section alters transcription factors' activity, increasing insulin sensitivity and FFA synthesis, finally exacerbating MASLD [35].

Toll-like receptor 4 (TLR4) is believed to play a role in the MASLD pathway in individuals with CHB. Among the ten types of TLRs that are vital for human innate immunity [35], TLR 4 is essential for initiating this response. TLR has been linked to MASLD through two distinct pathways, MyD88-dependent and MyD88-independent, both of which lead to the release of proinflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and type 1 interferon (IFN-1). Although bacterial endotoxin lipopolysaccharide (LPS) is typically the ligand activating TLR4, nonbacterial substances such as free fatty acids (FFAs) can also bind to it. Specifically, the FFAs palmitic acid (PA) and oleic acid predominantly interact with TLR4, activating the expression of proinflammatory cytokines in hepatocytes, adipocytes, and macrophages [36,37] (Figure 1). Several studies support the interruption of TLRs intracellular signaling pathway by HBV components. HBV polymerase inhibited TNF-α, TLR3, and TLR4-induced NF-κB signaling [38,39].

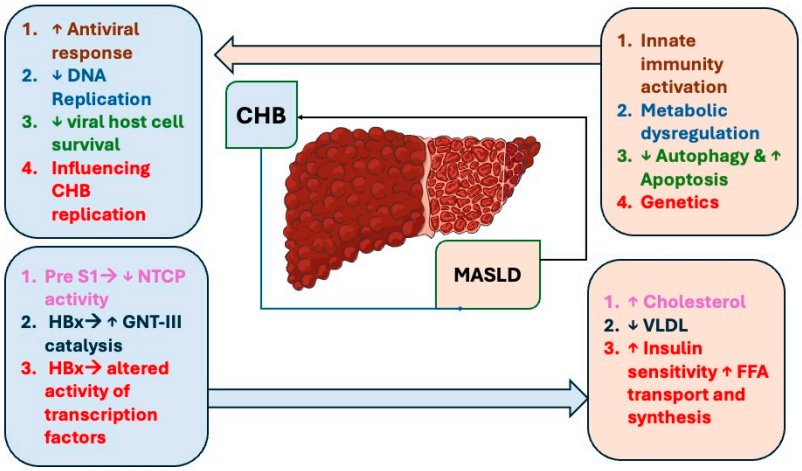

Figure 1. The interaction between MASLD and CHB. CHB: chronic hepatitis B; FFA: free fatty acid; GnT-III: β1,4-N-acetylglucosaminyltransferase-III; MASLD: Metabolic dysfunction-associated steatotic liver disease; NTCP: Na+-taurocholate cotransporting polypeptide; VLDL: very low-density lipoprotein.

5. Effect of MASLD on the Viral Load

The association between CHB, its viral load, and MASLD has been extensively studied. Patients with higher levels of HBV DNA appear less likely to develop MASLD than those with lower HBV DNA levels [40]. Additionally, individuals with hepatic steatosis tend to have lower levels of HBV DNA and hepatitis B e antigen (HBeAg) compared to those

without steatosis [31,41]. Conversely, those with MASLD are more likely to achieve HBsAg clearance [41]. This may be attributed to increased gene expression related to T-helper 17 cells, including cytokines like IL-21, which are abundant in patients with steatosis and may contribute to CHB clearance [42,43]. A recent meta-analysis by Zhang et al. [44] supports these findings.

Some studies, however, suggest that CHB may also stimulate lipid synthesis by activating key proteins involved in lipid production and FFA oxidization [45]. CHB has been shown to enhance FFA synthesis via FFA binding protein 5 and Acyl-CoA binding protein, which both play significant roles in FFA metabolism and synthesis due to their high affinity for Acyl-CoA and FFAs, with elevated levels observed in CHB transgenic mice [46]. Notably, significant upregulation of retinol-binding protein 1 (RBP1), sterol regulatory element binding protein 2 (SREBP2), ATP citrate lyase, and fatty acid synthase suggests CHB impacts genes related to lipid metabolism in these transgenic mice. CHB also influences the functionality of fatty acid binding protein 5 and acyl-CoA binding protein, that are crucial for FFA metabolism and synthesis [47]. Another proposed mechanism involves the upregulation of the hepatitis B X protein, which may promote FFA oxidation to maintain ATP balance and intracellular nicotinamide adenine dinucleotide phosphate levels, particularly during glucose deprivation. This pathway may also enable the survival of hepatocellular carcinoma cells under metabolic stress [31].

6. Effect of Coexistence of MASLD and CHB on Development of MASH and Liver Fibrosis

MASLD and CHB are progressive diseases that begin with inflammation and can advance fibrosis and cirrhosis. However, the effect of their coexistence on fibrosis and cirrhosis progression remains unclear. In a study of over 1000 CHB patients, those with MASH exhibited a higher degree of fibrosis than those without MASH [48]. Conversely, a recent study of 1496 CHB patients reported less severe fibrosis among those with MASLD [49]. Yet, two recent meta-analyses found no significant association between advanced fibrosis and the coexistence of CHB and hepatic steatosis [44,50] (Table 2).

Table 2. Effect of MASLD and CHB on liver fibrosis.

Study	Number	Concurrent	Effect on Fibrosis	Mechanism
Choi et al., 2020 [48]	1074	334	MASH was independently associated with higher liver-related outcomes (aHR: 1.62; 95% CI: 1.05–2.51; p = 0.03).	Accumulation of toxic lipid species induces ER stress and ROS, driving apoptosis and HSC activation.
Yao et al., 2024 [49]	1496	290	MASLD was independently associated with a lower risk of significant fibrosis (aOR: 0.61; 95% CI: 0.45–0.82; p = 0.001).	Steatosis may trigger TLR4-mediated innate immune responses that actively suppress HBV replication and HBsAg expression.
Zheng et al., 2021 [44]	28,648	9396	No significant difference in advanced fibrosis prevalence with or without steatosis (40.1% vs. 42.2%; Pooled OR: 0.87; 95% CI: 0.54–1.39).	In broad populations, HBV replication kinetics and immune clearance phases dominate the early fibrogenic drive, obscuring the impact of mild metabolic dysfunction.
Jiang et al., 2021 [50]	17,664	5228	Coexistence of steatosis did not significantly increase the risk of advanced fibrosis (Pooled OR: 0.68; 95% CI: 0.44–1.05).	The pro-fibrotic signaling induced by insulin resistance is counterbalanced by the steatosis-induced suppression of viral necroinflammation.

aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CHB, chronic hepatitis B; CI, confidence interval; ER, endoplasmic reticulum; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSC, hepatic stellate cell; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; ROS, reactive oxygen species; TLR4, toll-like receptor 4.

The degree of steatosis was also linked to the progression of fibrosis in patients with CHB. In a study by Huang et al. [51], the authors included 1081 CHB patients; 37.4% of the

cohort reported MASLD, and 24% had MASH. The presence of MASH predicted significant fibrosis (OR = 2.53) and severe fibrosis (OR = 1.83). In another cohort in which controlled attenuation parameter (CAP) was used to assess steatosis, a 15% increase in fibrosis risk was reported for every 10 dB/m increase in CAP in treatment-naive patients, and 7–8% in patients receiving treatment [52].

7. Effect of Coexistence of MASLD and CHB on HCC Development

HCC is a major cause of morbidity and mortality in the natural course of chronic liver diseases, especially in cases with cirrhosis, such as MASLD (with an annual incidence of 0.021% [53,54]), as well as in noncirrhotic CHB cases [55]. The effect of CHB and MASLD cooccurrence on HCC development is still under investigation (Table 3). Some evidence suggests an increased risk of HCC in patients with both CHB and MASLD compared to those with CHB alone [48]. In a recent meta-analysis by Mao et al. [41], hepatic steatosis was associated with a higher risk of developing HCC in patients with CHB. In contrast, findings from Li et al. [56] suggest that steatosis, may act as a protective factor against HCC in CHB patients, with a 10-year HCC risk of 3.7% for patients with steatosis versus 6.2% for those without. Additional studies using the CAP to assess steatosis found that higher CAP values correlated with a lower incidence of HCC [8,57].

Table 3. Impact of concurrent steatosis on HCC development in CHB patients.

Study	Number	Concurrent	Effect on HCC Risk	Mechanism
Mao et al. [41]	68,268	22,392	Increased risk OR: 1.59 (95% CI: 1.12–2.26)	Upregulation of TNF-alpha and IL-6 activates NF-κB and STAT3 pathways, promoting malignant survival.
Lin et al. [18]	1613	483	Increased HCC risk regardless of CMRF	Lipid peroxidation and DNA damage serve as independent carcinogenic drivers in CHB patients.
Li et al. [56]	6786	1605	Decreased risk 10-year risk: 3.7% vs. 6.2% (HR: 0.41, $p < 0.001$)	Steatosis may suppress HBsAg expression and CHB viral replication, reducing the primary viral "hit."
Oh et al. [57]	1823	565	Decreased aHR: 0.47 (for patients with high stiffness)	Lipid accumulation may trigger localized immune monitoring that clears pre-malignant hepatocytes.
Adali et al. [19]	535	187	Steatosis alone: Non-significant > 3 CMRFs: High Risk.	HCC risk is driven by CMRFs rather than isolated intrahepatic fat.
Huynh et al. [16]	952	275	Better survival in non-cirrhotic females with BMI > 23.	Higher BMI in specific subgroups may indicate better nutritional status or altered tumor microenvironments.

aHR, adjusted hazard ratio; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; CMRF, cardiometabolic risk factor; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; IL-6, interleukin-6; NF-κB, nuclear factor kappa B; OR, odds ratio; *p*, *p*-value; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor-alpha.

Regarding the relationship between BMI and HCC in patients with CHB, in a cohort of 4944 individuals, 3.1% developed HCC. Obesity was an independent risk factor for HCC development, with an aHR of 1.85 [58]. This was in alignment with another cohort of 350,608 Korean patients, where higher BMI was associated with increased risk of HCC in MASLD and CHB [59].

The mechanisms underlying HCC development include persistent liver inflammation, immune-mediated liver injury, and the subsequent upregulation of proinflammatory factors and cytokines such as TNFα, IL-6, leptin, adiponectin, and chemokines, which can occur in both CHB and MASLD [60]. TNF-α activates the nuclear factor kappa B (NF-κB) and c-Jun N-terminal Kinase signaling pathways, promoting the survival of malignant HCC cells and inhibiting apoptosis. IL-6, another key cytokine, plays a critical role in the

repair and replication of malignant cells by activating the signal transducer and activator of transcription 3 (STAT3) signaling pathway [61]. The progression of HCC may also be influenced by chemokines such as chemokine-like factor-1 (CKLF1), which is overexpressed in HCC and significantly associated with more advanced tumor stages, increased vascular invasion, and a poorer prognosis [62].

The signaling of the IL-6/STAT3 and C-C motif chemokine ligand-5 (CCL5) pathways can be activated by the patatin-like phospholipase domain-containing protein 3 (PNPLA3) polymorphism. In mutant mice, the 148 isoleucine to methionine variant (I148M) of PNPLA3 (PNPLA3-I148M) has been linked to the development of liver steatosis [63]. The proliferation of HCC cells can be promoted by the PNPLA3-I148M protein variant in malignant cells through the IL6/STAT3 pathway. This activation may also lead to the activation of stellate cells by upregulating CCL5 and collagen 1α1 expression (COL1A1) [64,65].

In CHB patients, as mentioned earlier, the HBx protein is a critical factor in the pathogenesis of HCC due to its carcinogenic properties. HBx promotes carcinogenesis by activating several pathways involved in HCC development, including mitogen-activated protein kinase (MAPK), NF-κB, IL-6/STAT3, and PI3K signaling pathways [66]. Additionally, HBsAg prevents NK cells from activating STAT3, which hampers CHB viral clearance and accelerates the progression of CHB into HCC [61,67]. One of the main cornerstones in tumor progression is the immunosuppressive microenvironment. In patients with CHB-related HCC, a higher peripheral blood neutrophil/lymphocyte ratio and increased Foxp3 + Treg cells are positively correlated with disease progression [68].

The connection between gut microbiota, its metabolites, and the incidence of steatosis and various malignancies [69] in hepatology and gastroenterology has been gaining increasing attention in recent years [70,71]. The progression of liver disease may be influenced by the microbiota due to the close anatomical proximity between the liver and gut, as well as theories regarding leaky gut syndrome and dysbiosis [70]. Research involving both animal models and human studies suggests that increased intestinal permeability (leaky gut) can lead to dysbiosis, which facilitates the entry of pathogen-associated molecular patterns (PAMPs) and gut microbiota-derived metabolites into the liver. This, in turn, can provoke hepatic steatosis, hepatitis, and the development of HCC [69]. PAMPs, such as lipopolysaccharide (LPS), are transported to the liver via the portal vein, where they are detected by TLRs (TLR4 and TLR9) in immune cells. This recognition triggers the production of various cytokines (IL-6, TNF- α, and IFN-γ), resulting in liver damage. Alterations in the normal composition of gut microbiota and dysbiosis have been observed in both MASLD [72] and CHB [73].

A recent study examined the key drivers of HCC in patients with MASLD. In this study, liver biopsies were performed to assess steatosis in 535 CHB patients [19]. The study found that the presence of steatosis alone in patients receiving treatment for CHB did not significantly increase the risk of HCC development. However, multiple CMRF were significantly associated with a higher incidence of HCC. These findings underscore the effectiveness of the new criteria for diagnosing MASLD. Additional independent risk factors for HCC in patients with dual etiology included advanced age, male gender, diabetes, and cirrhosis.

8. Effect of Metabolic Dysregulation on the CHB-Related HCC Diagnosis

Metabolic dysregulation refers to the imbalance in metabolic processes, including cellular signaling and energy production. The disturbance in these pathways contributes to various disease progression. As previously discussed, the relationship between HCC, CHB, and the disruption of hepatic lipid metabolism is complex. Zuo et al. [74] found significant differences in serum lipoprotein subfractions between healthy individuals and

CHB-related early HCC patients, indicating alterations in lipid metabolism. In patients with CHB-related early HCC, a significant correlation was observed between seruangiogenic factor angiopoietin-like protein 6 (ANGPTL6) and several serum lipoprotein subfractions, which showed markedly diverse changes.

ANGPTL6 has been shown to stimulate angiogenesis and endothelial cell migration in stomach cancer that produces AFP [75]. ANGPTL6 may also promote liver metastasis from colorectal cancer. Recently, ANGPTL6 has been linked to primary HCC, although its exact role remains unclear. Studies have reported higher serum ANGPTL6 expression in HCC patients compared to healthy individuals [75], leading to the hypothesis that it could serve as a diagnostic marker for HCC, with an accuracy of 71%. This suggests that alterations in lipid metabolism may be associated with higher serum ANGPTL6 expression. Future large-scale studies are necessary to confirm this hypothesis and determine whether ANGPTL6 can be validated as a diagnostic marker for HCC.

9. Relationship Between CHB and Metabolic Syndrome Components

9.1. CHB and Dyslipidemia

Dyslipidemia, which includes hypercholesterolemia or hypertriglyceridemia, is a known risk factor for atherosclerosis and can lead to cardiovascular and cerebral vascular disorders. CHB has been found to be inversely correlated with all components of the lipid profile, including cholesterol, triglycerides (TG), HDL-C, and low-density lipoprotein cholesterol (LDL-C), as reported by Meena et al. [76]. In a large-scale community-based cohort study involving 56,336 individuals, those who were seropositive for CHB showed decreased prevalence of hypertriglyceridemia and hypercholesterolemia [77]. Another study, which analyzed clinical data from 1330 medical center personnel, found that among 195 personnel diagnosed with CHB, blood levels of total cholesterol and HDL-C were lower compared to those without CHB [78].

A case–control study also indicated that individuals with CHB had significantly lower blood TG and HDL levels compared to healthy controls. This study further reported an inverse relationship between serum HBV-DNA levels and serum TG levels. Similar findings were observed in a cohort of 122 individuals with CHB who also had insulin resistance and elevated HBV-DNA levels [79]. However, a more recent report from Ghana [80], which included 29 patients with CHB, found an increase in the cardiovascular disease risk index. These patients had higher cholesterol and LDL levels, but lower HDL levels, compared to healthy individuals. The authors recommended monitoring patients with CHB for potential cardiovascular events.

9.2. CHB and Atherosclerosis

Although the relationship between atherosclerosis and CHB has been examined in the literature, no conclusive evidence establishes a strong link between the two diseases or identifies the underlying mechanism [81]. However, two studies using carotid duplex or pulse wave velocity to assess arteriosclerosis found that individuals with CHB did not have a higher risk of developing arteriosclerosis compared to healthy controls. Furthermore, patients with and without coronary artery disease had similar rates of CHB seropositivity [82,83]. Another large cohort study from Taiwan revealed no significant association between CHB seropositivity and morbidity or mortality related to atherosclerosis [84]. In contrast, Targher et al. [85] reported that MASH and CHB were linked to early arteriosclerosis, despite the small sample size. The authors used carotid intima-media thickness as an early indicator of atherosclerosis.

A recent genome-wide association study (GWAS) study [86] concluded that patients with CHB had a high risk of developing atherosclerosis and coronary artery disease, while showing a lower risk of cerebrovascular ischemic strokes.

Despite these studies suggesting a potential connection between CHB and atherosclerosis and, by extension, cardiovascular disease, the exact mechanism remains unclear. Several theories may explain this association. One possibility is CHB-induced steatosis, which could contribute to atherosclerosis and endothelial dysfunction, thereby promoting cardiovascular disease. Furthermore, the virus itself, in conjugation with a proinflammatory state, may cause oxidative damage, increasing the likelihood of atherosclerosis in CHB patients [87]. Moreover, patients with CHB exhibit reductions in protective factors such as paraoxonase-1 and aryl esterase activity, as well as a decrease in plasma free sulfhydryl groups and total antioxidant capacity, all of which contribute to increased susceptibility to atherosclerosis [88]. Furthermore, CHB patients with fibrosis often experience an enhanced immune response, which may elevate their risk for cardiovascular disease [86].

9.3. CHB and Insulin Resistance

Insulin resistance is a leading cause of metabolic syndrome and diabetes mellitus. In an earlier Taiwanese cohort, no significant difference in insulin resistance was found between individuals with CHB and healthy controls [89]. Furthermore, serum HBV-DNA levels did not correlate with the homeostatic model assessment of insulin resistance (HOMA-IR) index in individuals with CHB. The 10-year incidence of diabetes or glucose intolerance was similar between asymptomatic CHB patients and those without the infection. This study, which included 296 participants without diabetes at the initial check-up, indicated that asymptomatic CHB infection did not increase the risk of diabetes. In contrast, a Korean study identified a link between insulin resistance and long-term CHB. The authors suggested that patients with long-standing CHB should be closely monitored for insulin resistance and diabetes [90]. However, the evidence connecting CHB to insulin resistance and diabetes remains limited and inconclusive. Previous studies, however, have shown a strong correlation between poor glycemic management and liver cirrhosis, a condition often referred to as "hepatogenous diabetes" [91]. In a prospective cohort by Holstein et al. [92], which included 52 patients with biopsy-proven cirrhosis and a median follow-up period of 6 years, nearly 96% of the patients developed diabetes or impaired glucose tolerance during the follow-up. The authors used the term hepatogenous diabetes to describe this condition, noting that it differed from type-2 diabetes in that it had a lower percentage of patients with a family history of the disease, as well as fewer cases of cardiovascular and retinal complications. Additionally, Senoymak et al. [93] reported that insulin resistance was more evident in the CHB patients in their cohort, though there was no significant correlation between insulin resistance and HBV DNA levels. In a study examining CHB, MASLD, and insulin resistance, Ye et al. [94] concluded that the increased metabolic risk in patients with CHB was primarily driven by insulin resistance, which was strongly associated with both CHB and MASLD, rather than by hypertriglyceridemia. Specifically, HOMA-IR values were significantly higher in CHB patients with concurrent steatosis than in those without (e.g., 3.25 ± 1.52 vs. 1.84 ± 0.91; $p < 0.001$), indicating that the metabolic burden in this population is disproportionately driven by steatosis rather than by viral replication.

10. Effect of MASLD on the Response to Antivirals of CHB

Currently, there is no treatment available that can provide a permanent cure for patients with CHB. However, nucleotide analogs (NA) have proven effective in controlling HBV DNA viral load, thereby reducing the risks of developing fibrosis, cirrhosis, and HCC [95]. The same treatment protocols used for patients with isolated CHB should be

applied to those with MASLD and CHB. However, the clinical evaluation of liver biochemical tests and viral load may be influenced by the presence of MASH, as it is associated with elevated liver enzymes and reduced HBV DNA levels [29]. It has been reported that CHB patients with MASLD may exhibit a lower response to NA compared to those with CHB alone. According to Chen et al. [96], steatosis not only detected the undetectable HBV DNA rates but also affected the normalization of alanine aminotransferase (ALT) levels in patients on entecavir-based regimens. Similar findings were reported in two meta-analyses of CHB patients receiving antiviral therapy [50,97]. While some conflicting studies have suggested comparable responses to antiviral therapy in patients with or without steatosis [98,99] (Table 4), it is advisable for hepatologists to screen for MASLD in patients with CHB. This is particularly important because persistent inflammation and viral activity can ultimately lead to fibrosis, cirrhosis, and HCC (Figure 2).

Table 4. Impact of MASLD on the clinical response to antiviral therapy.

Study	Number	Effect on Treatment Response
Chen et al. [96]	170	Impaired Response: Elevated CAP values predicted failure to achieve undetectable DNA and hindered ALT normalization.
Li et al. [98]	1212	Hepatic steatosis was not an independent predictor of virological or biochemical response.
Charatcharoenwitthaya et al. [99]	323	Steatohepatitis did not significantly alter the rates of virological suppression or HBeAg loss.
Huang et al. [11]	4084	MASLD was associated with a higher probability of HBsAg seroclearance in treatment-naive patients.
Adali et al. [19]	535	While steatosis was neutral for response > 3, CMRFs significantly increased long-term HCC risk despite AVT.

ALT, alanine aminotransferase; AVT, antiviral therapy; CAP, controlled attenuation parameter; CMRF, cardiometabolic risk factor; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.

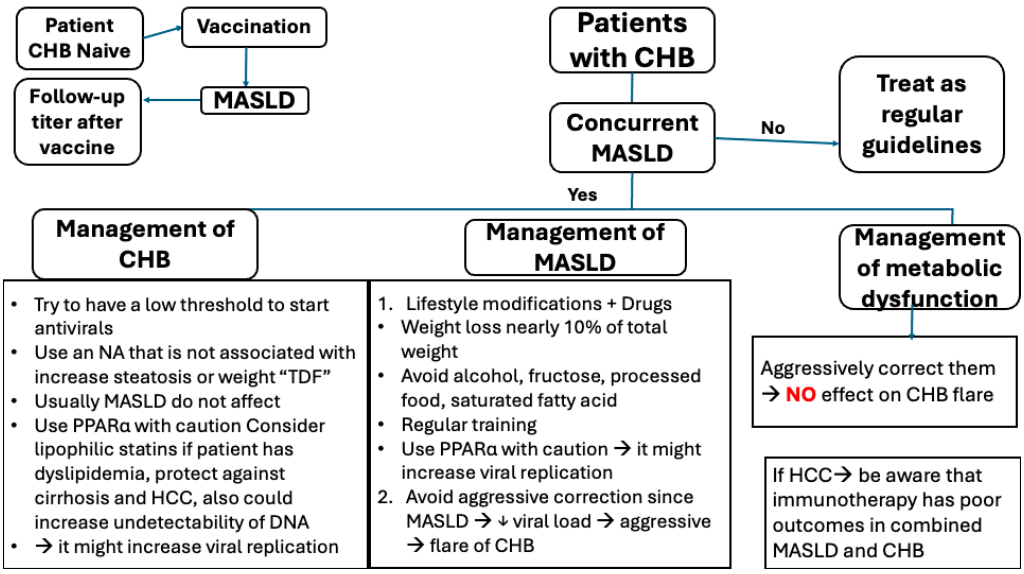

Figure 2. Proposed algorithm for the management of combined CHB and MASLD. CHB: chronic hepatitis B; MASLD: Metabolic dysfunction-associated steatotic liver disease; HCC: Hepatocellular carcinoma; TDF: tenofovir disoproxil fumarate; PPARα: Peroxisome proliferator-activated receptor α.

The mechanism behind the relationship between MASLD and HBV replication mainly involves metabolic disturbances. In patients with MASLD-CHB, lower baseline HBV DNA levels are primarily due to a transcriptional bottleneck; hepatic steatosis reduces key host transcription factors, especially hepatocyte nuclear factor 4 alpha, which the virus requires

for activation of the core promoter. Additionally, oxidative stress from lipid buildup produces reactive oxygen species (ROS), which can further impair the virus's polymerase function and stability. Meanwhile, consistently high ALT levels, even when viral activity is well-controlled with medications like nucleos(t)ide analogues, are driven by lipotoxicity-related inflammation and cell death that occur independently of viral suppression [58].

11. Effect of CHB Antivirals on MASLD

Few studies in the literature have explored the effect of CHB antivirals on MASLD or hepatic steatosis. One study compared body fat mass and visceral fat area across three groups: (1) treatment of naive CHB patients, (2) CHB patients who had been on NA for 7 years, and 3 healthy individuals. The authors found that both body fat mass and visceral fat area were higher in the CHB group receiving NA treatment, and these patients achieved undetectable HBV DNA levels. However, it remained unclear whether these changes were due to the reduction in viral load or the direct effects of the antiviral treatments itself [100]. Another study compared the effects of two antiviral drugs, tenofovir disoproxil fumarate (TDF) and entecavir, on lipid profiles. The study included 348 CHB patients and found that those on TDF were more likely to experience reductions in cholesterol and LDL levels compared to those on entecavir [101]. TDF was later compared with tenofovir alafenamide (TAF) in patients transitioning from TDF to TAF. The results showed that patients switching to TAF had significantly higher cholesterol and LDL levels, with the dyslipidemia rate increasing from 33% to 39% after the switch [102]. Additionally, this group of patients gained more than 5% of their baseline weight after switching [103]. Based on these studies, TDF appears to have lipid-lowering effects, whereas TAF is associated with weight gain and worsening lipid profile parameters, potentially contributing to the development or progression of steatosis.

12. Lipid-Lowering Agents and Viral Replication

Peroxisome proliferator-activated receptor (PPARα) agonists should be used cautiously in patients with CHB. It has been reported that PPARα agonists are associated with increased HBV DNA replication [104]. The safety of other lipid-lowering agents, such as statins, has also been a subject of controversy, particularly in patients with viral hepatitis, including those with CHB.

In patients with CHB only, statins could help by inhibiting the mevalonate pathway, which restricts the production of the cholesterol needed for HBV envelope formation, and also by suppressing its oncogenic signaling pathway. However, in patients with concurrent MASLD and CHB, statins could provide a synergistic effect by inhibiting both the viral and metabolic drivers. Statins act as metabolic stabilizers by reducing lipotoxicity-induced oxidative stress, thereby decreasing the hepatitis burden and inhibiting disease progression through the downregulation of TNF-alpha and IL-6 levels [15,105].

In 2013, a case report was published describing reactivation of CHB following the use of atorvastatin [106]. However, a more recent clinical trial that atorvastatin, when used in combination with TDF, led to a reduction in the viral load of CHB [107]. In this study, a cohort of 40 patients was divided into two groups: one received 40 mg of atorvastatin along with 300 mg of TDF, while the other group received a placebo with TDF. After three months, 50% of patients in the atorvastatin group had an undetectable viral load, compared to 30% in the placebo group.

In a meta-analysis assessing the protective effects of statins against cirrhosis, statins were associated with a 42% reduction in the incidence of cirrhosis in both CHB and chronic hepatitis C (CHC) patients [108]. Fibrogenic cytokines such as transforming growth factor-ß, platelet-derived growth factor, and connective tissue growth factor are critical to the

progression of liver cirrhosis. One proposed mechanism by which statins may help prevent cirrhosis is their ability to suppress the production of fibrogenic cytokines [109,110]. Statins may also improve hepatic microcirculation and liver fibrosis by increasing the expression of the Kruppel-like factor 2 [111]. Furthermore, statins could exert an anti-CHB effect by inhibiting both cholesterol production and HBV replication [112].

Another meta-analysis found that statins reduced the risk of HCC in patients with CHB and CHC by 55% [113]. In a study that exclusively recruited patients with CHB, statins effectively decreased the incidence of HCC, leading the authors to recommend their use in CHB patients with dyslipidemia [114]. In addition to their anti-CHB effects, the authors proposed several mechanisms through which statins could help prevent HCC. One mechanism involves inhibiting the downstream products of the mevalonate pathway, which are essential for the growth of cancerous cells [115]. In patients with CHB alone, the protective effect of statins is primarily mediated through the inhibition of the mevalonate pathway and direct viral suppression [112,115]. Another mechanism is the reduction in protooncogenic transcription factor Myc activation, which is also linked to HCC. This occurs through statin-induced disruption of the mitochondrial membrane [116]. The type of statin, lipophilic versus hydrophilic, and their use in CHB and MASH has generated some interest. A 10-year risk study of HCC compared the risk of HCC between patients taking lipophilic and hydrophilic statins. For those with concurrent steatosis and CHB, statins offer a synergistic benefit by addressing both viral activity and metabolic drivers of oncogenesis, such as chronic steatohepatitis and insulin resistance. It was found that lipophilic statins significantly reduced the risk of HCC in a Swedish cohort, whereas hydrophilic statins conferred no protective benefit [117]. Another study investigated the role of statins by etiology and reported that lipophilic statins provided significant protection against HCC associated with CHB, MASH, and CHC. In contrast, hydrophilic statins were only protective against MASH-related HCC [118].

13. Effects of MASLD Correction on the CHB Viral Load

As previously discussed, the inverse relationship between MASLD and CHB viral load raises concerns about the treatment of MASLD. While there is no clear consensus or formal guidelines against addressing MASLD, it would be illogical to oppose its correction. However, it is recommended to closely monitor liver enzymes during the treatment of MASLD, along with continuous monitoring of CHB DNA levels throughout the correction process. Without substantial evidence, this recommendation remains theoretical and holds no clinical value at present [34,38].

14. Effect of MASLD on CHB-Related HCC Immunotherapy

The response of patients with HCC to immunotherapy has been reported to be lower in those with MASH [119]. A retrospective study by Han et al. [14] investigated the impact of MASLD on CHB-related HCC. The study included 155 patients who received monoclonal antibodies targeting PD-1/PD-L1. Patients with both MASLD and CHB had a shorter survival time of 6.9 months, compared to 9.3 months for those with CHB alone. Additionally, these patients experienced more disease progression (57.9% vs. 37.6%) and poorer disease control rates (42.1% vs. 62.4%). This diminished immune response is presumably driven by the distinctive immune landscape of the steatotic liver. The same concept was also reported in patients with MASH and cholangiocarcinoma, but the HbsAg status was not included in the study [120]. Chronic metabolic inflammation associated with MASLD facilitates the accumulation of non-conventional CD8+PD-1+ T cells, which can contribute to anti-tumor functions despite their contribution to the hepatocellular injury. Also, the increase in regulatory T cells and myeloid-derived suppressor cells in MASLD

can result in immunosuppressive effects that reduce the therapeutic efficacy of immune checkpoint blockade [119].

15. Effect of MASLD on Hepatitis B Virus Vaccination

The hepatitis B vaccine has significantly reduced the rate of new infections, thereby lowering the incidence of HCC. A Canadian study included 68 MASLD patients seronegative for HBsAg who completed three doses of the vaccine [120]. These patients were categorized according to body mass index (BMI) into low-risk or medium-to-high-risk groups for obesity. Anti-HBs titers were measured 1–3 months after vaccination. The study found significantly lower titers in MASLD patients with medium-to-high obesity risk. The authors concluded that obese patients with MASLD exhibit a significantly lower immune response to the hepatitis B vaccine.

16. Conclusions

The existing body of research suggests a negative correlation between MASLD and CHB. However, recent changes in the definition and the inclusion of CMRF, particularly those related to high lipid profiles associated with hepatic steatosis, have sparked debate over this correlation. This relationship requires further investigation to clarify and substantiate, especially given that CHB increases FFA synthesis. The effect of the coexistence of CHB and MASLD on the progression of liver fibrosis remains unclear. However, it is now evident that both conditions can increase the risk of HCC. Certain drugs, such as lipophilic statins, have shown protective effects against cirrhosis and HCC in patients with both diseases. The choice of antiviral treatment for patients with CHB should be individualized, with consideration given to the presence of MASLD, as some antivirals, such as TAF, have been associated with weight gain and the exacerbation of steatosis. Future studies are needed to assess the impact of correcting MASLD on viral load and whether this could lead to disease reactivation or flare-ups. Finally, the introduction of new definitions and diagnostic criteria has made retrospective application of these criteria less accurate than prospective studies. Therefore, new prospective studies that use the new criteria to diagnose MASLD in CHB patients need to be added to the existing body of evidence.

Author Contributions: Conceptualization, H.H.A. and M.E.-K.; Writing—original draft, A.T., and A.A.M. Writing—review and editing, H.H.A. and M.E.-K. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by Grants in aid for Scientific Research C, 23K06575 and the Research Program on Hepatitis B from AMED (grants number: 26fk0310532s0102; and 26fk0310528s0102) to Hussein H. Aly.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AFP: alpha-fetoprotein; ANGPTL6: angiogenic factor angiopoietin-like protein 6; ATP: adenosine triphosphate; CAP: controlled attenuation parameter; CCL5: C-C motif chemokine ligand-5; CHB: chronic hepatitis B; CKLF1: chemokine-like factor-1; CMRF: cardiometabolic risk factors;

COL1A1: collagen 1α1; FFA: free fatty acids; GnT-III: β1,4—N—acetylglucosaminyltransferase—III; GWAS: genome-wide association study; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HBx: hepatitis B X protein; HCC: hepatocellular carcinoma; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; IFNsI: type 1 interferon; IL-6: interleukin 6; IL-21: interleukin-21; LDL-C: low-density lipoprotein cholesterol; LPS: lipopolysaccharide; MAFLD: metabolic dysfunction-associated fatty liver disease; MAPK: mitogen-activated protein kinase; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; MetALD: a classification of liver disease for individuals with MASLD and alcohol consumption beyond specified limits; MyD88: myeloid differentiation primary response 88; NAFLD: nonalcoholic fatty liver disease; NF-κB: nuclear factor kappa B; NTCP: Na+—taurocholate cotransporting polypeptide; PA: palmitic acid; PAMPs: pathogen-associated molecular patterns; PI3K: phosphoinositide 3-kinase; PNPLA3: patatin-like phospholipase domain-containing protein 3; RBP1: retinol-binding protein 1; SLD: steatotic liver disease; SREBP2: sterol regulatory element binding protein 2; STAT3: signal transducer and activator of transcription 3; TG: triglycerides; TLR: Toll-like receptor; TLR4: Toll-like receptor 4; TNF-α: tumor necrosis factor α; Treg: regulatory T cells; VLDL: very low-density lipoprotein.

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