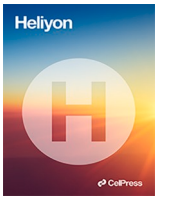
Heliyon 9 (2023) e13113

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Hepatitis B virus infection combined with nonalcoholic fatty liver disease: Interaction and prognosis

Lili Liu [a], Hong Li [a], Yang Zhang [b], Jing Zhang [a,**], Zhenhuan Cao [a,*]

[a] The Third Unit, Department of Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, China
[b] Biomedical Information Center, Beijing Youan Hospital, Capital Medical University, Beijing, China

ARTICLE INFO

Keywords:
Nonalcoholic fatty liver disease
HBV infection
Antiviral efficacy
Liver fibrosis
Hepatocellular carcinoma

ABSTRACT

Hepatitis B virus (HBV) infection is still one kind of the infectious diseases that seriously threaten human health. Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide. HBV infection complicated with NAFLD is increasingly common. This review mainly describes the interaction between HBV infection and NAFLD, the interaction between steatosis and antiviral drugs, and the prognosis of HBV infection complicated with NAFLD. Most studies suggest that HBV infection may reduce the incidence of NAFLD. NAFLD can promote the spontaneous clearance of hepatitis B surface antigen (HBsAg), but whether it affects antiviral efficacy has been reported inconsistently. HBV infection combined with NAFLD can promote the progression of liver fibrosis, especially in patients with severe steatosis. The outcome of HBV infection combined with NAFLD predisposing to the progression of HCC remains controversial.

1. Introduction

At present, there are about 250 million chronic hepatitis B virus (HBV) infected people worldwide, especially in Africa and East Asia, with a prevalence of more than 8% [1]. It is worth noting that chronic HBV infection is the main cause of liver cirrhosis and liver cancer in China, and HBV-related liver disease deaths (308,000 deaths per year) [2]. Although with the application of hepatitis B vaccine, nucleotide analogues (NA) and interferon, the number of HBV infected patients has dropped significantly, but due to the existence of covalently closed circular DNA, HBV cannot be completely eliminated, functional cure is currently the highest treatment goal that can be achieved [3,4,5]. A recent study in the United States showed that NAFLD is the only liver disease with an increasing prevalence over the past 30 years [6]. Another study showed that the prevalence of NAFLD in Asia is similar to that in Western countries [7]. Nonalcoholic fatty liver disease (NAFLD), with a global prevalence of 25.24%, has become the most common chronic liver disease. There is no approved drug [8]. The proportion of nonalcoholic steatohepatitis (NASH) patients with inflammatory

Abbreviations: aHR, adjusted hazard ratio; AVT, antiviral therapy; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein-cholesterol; HR, hazard ratio; HS, hepatis steatosis; LDL-C, low-density lipoprotein cholesterol; NA, nucleos(t)ide analogue; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; non-HDL-C, non-high-density lipoprotein-cholesterol; NR, not reported; OR, odds ratio; PEG-IFN, pegylated interferon; TAF, tenofovir alafenamide; TDF, tenofovir; TLR4, Toll-Like Receptor 4.

* Corresponding author.
** Corresponding author.
E-mail addresses: zjyouan@ccmu.edu.cn (J. Zhang), caozhenhuanyu@mail.ccmu.edu.cn (Z. Cao).

https://doi.org/10.1016/j.heliyon.2023.e13113
Received 3 November 2022; Received in revised form 7 January 2023; Accepted 18 January 2023
Available online 20 January 2023

activity in NAFLD population can reach 59.10%, which is a high risk group for developing liver cirrhosis and liver cancer [8]. Paik et al. study revealed that globally from 2012 to 2017, viral hepatitis was the most common cause of death from liver disease, and NAFLD was the most rapidly growing contributor to liver mortality and morbidity [9].

It was noticed that patients with co-morbidities of CHB and NAFLD are not uncommon and therefore many studies on both diseases have emerged. In a Chinese cohort study, 2393 chronic hepatitis B (CHB) patients were followed up for 4429 person-years, of whom 283 progressed to NAFLD, with an incidence rate of 63.89/1000 person-years [10]. Another large North American cohort study showed that the incidence of CHB patients with NAFLD was 31.4% (13.1% had steatohepatitis) [11]. A meta-analysis by Zheng et al. including 53 studies showed that the incidence of NAFLD in CHB patients was 32.83% [12].

To sum up, it can be seen that the number of patients with chronic HBV infection and NAFLD is large, and the long-term prognosis of each disease is poor. At present, the coexistence of the two diseases is becoming more and more common. The interaction between HBV infection and NAFLD, the interaction between steatosis and antiviral drugs, and the prognosis of HBV infection complicated with NAFLD are not clearly concluded. We hence present a review and analysis of the above aspects with the aim of benefiting patients with both disease co-morbidities and paying attention to screening for NAFLD and selection of antiviral drugs in patients with CHB.

2. Interaction between HBV infection and NAFLD

2.1. Effect of HBV infection on the incidence of NAFLD

Most studies suggest that HBV infection reduces the incidence of NAFLD (Table 1). In a large-scale cohort study of Korean healthy population, 83,339 patients were divided into hepatitis B surface antigen (HBsAg)-positive group and HBsAg-negative group, screend for NAFLD by ultrasonography annually or biennially, and followed up for 484,736.1 person-years [13]. After adjusting for confounders such as age, sex, follow-up time, alcohol intake, and body mass index (BMI), the prevalence of NAFLD in the HBsAg-positive group was significantly lower than that in the HBsAg-negative group (adjusted hazard ratio [aHR] = 0.83, 95% confidence interval [CI] 0.73–0.94) [13]. A study from Taiwan, China, also illustrated that HBsAg positivity was negatively associated with NAFLD, especially for subjects with BMI>22.4 kg/m^2 and age>50 years [14].

Similarly, a cross-sectional demographic study in Hong Kong, China also suggested that HBV infection was inversely associated with the occurrence of NAFLD (adjusted odds ratio [aOR] = 0.42, 95%CI 0.20–0.88) [15]. Yu et al. established a research cohort of 2255 middle to older-aged patients, and found that HBV-infected patients had a lower risk of new and persistent hepatic steatosis (HS) by ultrasound examination (OR = 0.54), while HBsAg clearance increased the risk of HS by 1.41-fold (95% CI 1.12–1.79) [16]. In addition to the negative correlation between serum HBsAg and the occurrence of NAFLD, liver biopsy results of 3212 Chinese CHB patients showed that intrahepatic HBsAg positivity was an independent factor in reducing the risk of steatosis (aOR = 0.90, 95% CI 0.84–0.97) in multivariate analysis [17]. The results of a meta-analysis by Keikha et al. showed that HBV infection was negatively associated with hepatic steatosis, but not significant (OR = 0.91, 95% CI 0.74–1.13) [18].

The above studies all suggest that the prevalence of NAFLD in HBsAg-positive population is lower, which may be related to the involvement of HBV in lipid metabolism in the liver. It was found that HS was positively correlated with the level of triglyceride and low-density lipoprotein cholesterol (LDL-C) and negatively correlated with HBV infection, suggesting that HBV may have the effect of neutralizing lipid metabolism [19]. Results of a Korean cohort study of non-cirrhotic and non-diabetic adults (n = 62,287) with a 4.46-year follow-up showed that serum HBsAg positivity was negatively correlated with development of hypercholesterolemia, high LDL-C triglyceride, and high non-high-density lipoprotein-cholesterol (non-HDL-C) (aHR = 0.71, 95%CI 0.64–0.79; 0.83 [0.78–0.89]; 0.61 [0.54–0.70]; 0.69 [0.63–0.75]; respectively) [20]. Similarly, the annual physical examination data from Taiwan, China also showed that the levels of triglyceride and LDL-C in HBV-infected patients were significantly lower than those in non-HBV-infected patients (OR = 0.7, 95%CI 0.6–0.9; 0.8[0.7–0.9]) [21]. These studies suggest that HBV has a negative regulatory role in lipid metabolism.

However, basic studies based on cell and mouse models have shown that HBV could induce complex changes in hepatic lipid metabolism, not only increasing lipid breakdown, but also enhancing lipid production [22]. For example, HBV could activate the expression of some key lipid and cholesterol production-related proteins, and upregulated fatty acid oxidation and bile acid synthesis.

Table 1
Effect of HBV infection on the incidence of NAFLD.

Research type	Country	Number of patients	HBV marks	HR or OR (95%CI)	Reference
Cohort study	Korea	83,339	HBsAg positive	0.83(0.73–0.94)	**Joo et al** [13]
Cohort study	China	2255	HBsAg positive	0.54(0.43–0.68)	**Yu et al** [16]
Cross-sectional study	China	1013	HBsAg positive	0.42(0.20–0.88)	**Wong et al** [15]
			HBeAg positive	2.89 (0.28–29.6)	
			HBV DNA (log IU/mL)	0.69 (0.34–1.39)	
Cohort study	China	33,439	HBsAg positive	0.70(0.64–0.76)	**Cheng et al** [14]
Cross-sectional study	China	3212	intrahepatic HBsAg positive	0.90(0.84–0.97)	**Wang et al** [17]
A systematic review and meta-analysis	China[a]	37,635	HBsAg positive	0.91(0.74–1.13)	**Keikha et al** [18]

Abbreviations: CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

[a] USA, Turkey, South Korea, Pakistan, Israel, Italy.

Hepatitis B virus X protein was an important regulator of hepatic steatosis, and hepatitis B virus X promoted hepatic lipid deposition and induced steatosis and apoptosis by upregulating the gene expression of various lipogenic enzymes [23,24,25]. The relationship between HBV and lipid metabolism is complex. More clinical and basic research is needed to determine whether consistent dyslipidemia exists in peripheral blood and hepatocytes during HBV infection.

2.2. Effects of NAFLD on HBV-infectioned patients

2.2.1. Effect of NAFLD on spontaneous HBsAg clearance

Most current studies suggest that HS is conducive to the spontaneous clearance of HBsAg. A study led by Chu et al. in Taiwan, China (54 HBsAg carriers with HBsAg seroclearance and 108 HBsAg carriers with HBsAg persistence) found that moderate (OR = 3.22, P = 0.017) and severe (OR = 3.87, P = 0.041) steatosis were positively correlated with spontaneous HBsAg clearance, whereas mild steatosis had no significant correlation with HBsAg clearance (OR = 1.76, P = 0.157) [26]. Subsequently, the research team studied spontaneous HBsAg clearance in inactive HBsAg carriers and found that subjects with HS were significantly younger at HBsAg clearance than those without (48.7 years vs 53.4 years, P = 0.001), but were more likely to have abnormal AST and ALT, tending to be liver cirrhosis [27]. A large cohort study by Li et al. (6786 Asian CHB patients, not receiving antiviral therapy) found that 10-year cumulative spontaneous HBsAg clearance was significantly higher in CHB patients combined fatty liver than in CHB patients without fatty liver (15.91% vs 11.84%, P = 0.003) [28]. Another study showed that CHB patients with negative HBV DNA were followed up for 3 years, steatosis was strongly correlated with spontaneous HBsAg clearance (hazard ratio[HR] = 3.25, 95%CI 1.28–8.24) [29]. A cohort study of 2385 HBsAg-positive Taiwanese civil servants (91.8% of patients not receiving antiviral therapy) followed 35,603.1 person-years, and 628 individuals achieved HBsAg clearance, which found that HS may have promoted HBsAg clearance (sub-distribution hazard ratio = 1.27, 95%CI 1.07–1.50) [30]. The Turkish study also showed that HS was an independent predictor of spontaneous HBsAg seroconversion in hepatitis B e antigen (HBeAg)-negative CHB patients (OR = 2.07, P = 0.03), and patients with mild HS were easy to achieve HBsAg seroconversion [31].

Conversely, there are studies that do not consider NAFLD to have an effect on spontaneous HBsAg clearance. A Korean study (HBV DNA-negative CHB patients, n = 720) with 3-year follow up found no correlation between HS and spontaneous HBsAg clearance (P = 0.518) [32].

In conclusion, most studies suggest that NAFLD is a favorable factor for spontaneous clearance of HBsAg. To more deeply understand the relationship and mechanisms between HBV and NAFLD, experts have conducted studies in animal models and cells (Table 2). Studies in HBV-immunocompetent mouse and HBV transgenic mice (high-fat diets) found that steatosis inhibited HBV replication, but HBV replication did not affect metabolic characteristics [33,34]. To some extent, NAFLD accelerates the liver disease of the mice carrying HBV [35]. The intrinsic mechanism may be enhanced T-cell response and TLR4-mediated innate immune response [36,37]. It is worth noting that although patients achieved HBsAg clearance, we should pay more attention to the poor long-term prognosis of patients, such as liver fibrosis and hepatocellular carcinoma (HCC).

2.2.2. Effect of NAFLD on antiviral efficacy in patients with CHB

Whether NAFLD affects the antiviral efficacy of CHB, including ALT normalization, HBV DNA suppression, HBeAg seroconversion, and HBsAg clearance, is still controversial. Some studies showed that NAFLD adversely affects antiviral efficacy, and some studies showed that NAFLD has a favorable effect on antiviral treatment, while more studies showed that NAFLD does not affect antiviral efficacy.

A Chinese study included 213 CHB patients (30.5% patients combined with HS) treated with entecavir (ETV), with lower rates of HBV-DNA supression (47.7% vs 58.8%, P = 0.01), HBeAg seroconversion (15.4% vs 15.5%, P = 0.28) and ALT normalization (40.0% vs 43.9%,P = 0.11) in those with HS at 24 weeks, and it was suggested that HS was an independent factor for poor response to ETV therapy [38]. A Korean study of 334 CHB patients (43.7% patients combined with HS) treated with ETV or tenofovir (TDF) showed a higher cumulative incidence of HBeAg loss in the no-combined hepatic steatosis group compared to the combined hepatic steatosis group (log-rank, P = 0.022) [39]. Another Korean multicenter retrospective study included 1282 treatment-naïve CHB patients on

Table 2
Studies of HBV and NAFLD in animal models and on cells.

Models	Key Finding	Reference
HBV-immunocompetent mouse model (high-fat diet)	Non-alcoholic hepatic steatosis inhibited HBV replication, includind HBV DNA and HBV-related antigens. But HBV replication did not alter lipid metabolism.	**Hu et al** [33]
HBV genotype B transgenic mouse (high-fat diets)	This model reduces the HBV viral factors but not the metabolic and histologic features.	**Zhang et al** [34]
HBV transgenic mice (high-fat diets)	NAFLD accelerates the liver disease of the mice carrying HBV to some extent.	**Lu et al** [35]
Patients with hepatitis B and NAFLD, mouse model of HBV and NAFLD	Enhanced T-cell responses contribute to the inhibition of HBV replication.	**Patel et al** [36]
HBV transgenic mice (high-fat diet), HepG2.2.15 cells (different concentrations of Stearic Acid)	Saturated Fatty Acids or Lipopolysaccharide activates TLR4, in vivo and in vitro, which initiates the TLR4/Myeloid differentiation factor 88 signaling and the production of proinflammatory cytokines. The TLR4-mediated innate immune response may contribute to the inhibited HBV replication.	**Zhang et al** [37]

Abbreviations: HBV, hepatitis B virus; NAFLD, nonalcoholic fatty liver disease; TLR4, Toll-Like Receptor 4.

antiviral therapy (tenofovir alafenamide [TAF] n = 270, TDF n = 617, ETV n = 395), and the results of multivariate analysis indicated that fatty liver was an independent factor for the reduction of ALT normalization rate (HR = 0.75, 95%CI 0.61–0.94) [40]. In addition, 89 HBeAg-positive CHB patients treated with pegylated interferon (PEG-IFN) for 48 weeks, and the rate of HBV DNA suppression at the end of 48 weeks of treatment in patients without steatosis did not differ from that in patients with steatosis [41]. However, at 48 weeks after drug discontinuation, the rate of HBV DNA suppression was higher in patients without steatosis than in patients with steatosis, and multivariate analysis indicated that steatosis was an unfavorable factor for sustained viral response (0R = 0.012,P = 0.02) [41].

In contrast, some studies have shown that patients with HS are more likely to achieve HBsAg clearance. In an international multicenter cohort study, 4769 treatment-naïve CHB patients were treated with ETV or TDF with a median follow-up of 5.16 years, and 58 patients eventually achieved HBsAg clearance with an annual incidence of 0.22% and a 10-year cumulative incidence of 2.11% [42]. Fatty liver was a baseline predictor of HBsAg clearance (adjusted subdistribution hazard ratio = 1.84, 95%CI 1.03–3.29) [42].

More studies have shown that NAFLD did not affect antiviral efficacy. In a retrospective study of 555 CHB patients (33.7% patients combined with NAFLD) treated with lamivudine, adefovir, ETV or TDF, multivariate analysis showed that NAFLD was not independently associated with HBV DNA suppression (HR = 1.06,P = 0.71) and ALT normalization (HR = 1.04,P = 0.86) [43]. Similarly, another retrospective multicenter cohort study showed no effect of NAFLD on HBV DNA suppression in CHB patients treated with ETV or TDF [44]. In addition to HS having no effect on HBV DNA suppression in CHB patients treated with NA, there are studies showing that steatosis also has no effect on HBV DNA suppression in CHB patients treated with PEG-IFN. In a Turkish study of 140 CHB patients (42 HBeAg-positive and 98 HBeAg-negative) receiving antiviral therapy (55.7% receiving PEG-IFN and 44.3% receiving PEF-IFN combined with lamivudine), there was no difference in HBV DNA suppression rates between patients with or without steatosis (36.2% vs 31.5%, P > 0.05 in HBeAg-negative group; 39.6% vs 33.3%, P > 0.05 in the HBeAg-positive group) [45]. In addition, in a retrospective study in Taiwan, China, 196 HBeAg-positive CHB patients received NA monotherapy with a median treatment and follow-up time of 24.3 months and 54.9 months, respectively, which showed no significant effect of hepatic steatosis on HBeAg seroclearance (54.9% vs. 57.4%, P = 0.830) [46].

2.2.3. Effect of antiviral drugs on hepatic steatosis in CHB patients

There were relatively few studies on whether antiviral drugs aggravate steatosis in CHB patients. A cross-sectional study of HBV infected men (untreated group, n = 30; ETV or adefovir treated for 7 years group, n = 50) and healthy men (control group, n = 30) matched by age and BMI showed that body fat mass and visceral fat area was significantly higher in CHB men treated with ETV or adefovir for 7 years than in the untreated group, which suggested that long-term oral administration of NAs may increase body fat mass and visceral fat area of CHB men through virological suppression [47]. A retrospective cohort study in North America that included 348 patients with CHB (72% receiving TDF and 28% receiving ETV) was more likely to show decreases in hypercholesterolemia and LDL-C in patients treated with TDF compared to those receiving ETV [48]. Similarly in a Korean study, CHB patients treated with TDF showed significant decreases in hypercholesterolemia and triglyceride compared to TAF [49]. In a retrospective multicenter study, CHB patients who switched from TDF to TAF treatment had significantly higher hypercholesterolemia, HDL-C, LDL-C, non-HDL-C, and

Table 3
Effect of hepatic steatosis on the progression of liver fibrosis in CHB patients.

Number of patients	Country	Treatment(proportion of treated patients); Therapy duration(years)	Follow-up (years)	OR (95%CI)	Reference
Total: 330 48.8% combined steatosis	China	Naïve	3	2.38 (1.23–4.60)[a]	Mak et al. [29]
Total: 1606 40.8% combined steatosis	China	NAs (55.9%); 6.3	NR	3.60 (1.21–10.75) (treatment-naive)[b] 1.95 (1.06–3.61) (3-year treatment)[b]	Seto et al. [58]
Total: 459 NR	China	NAs (51.2%); 8.4	10	2.90 (0.95–8.82) (treatment-naive) 7.80 (2.27–26.78) (treatment)	Mak et al. [60]
Total: 720 44.9% combined steatosis	Korea	Naïve	3	1.09 (0.64–1.85)	Chang et al. [32]
Total:614 47.9% combined steatosis	Malaysia	Antiviral therapy (23.8%) 6.7	3.75	1.96 (1.25–3.06)	Wong et al. [63]
Total: 1081 37.4% (24.0%) combined steatosis (steatohepatitis)	China	Naïve	NR	0.83 (0.65–1.07) (steatosis) 2.53 (1.52–4.21) (steatohepatitis)	Huang et al. [61]
Total: 256 38% (18%) combined steatosis (steatohepatitis)	Thailand	Naïve	NR	1.31 (0.79–2.17) (steatosis) 10.0 (2.08–48.5) (steatohepatitis)	Charatcharoenwitthaya et al. [62]

Abbreviations: CHB, chronic hepatitis B; CI, confidence interval; NAs, nucleos(t)ide analogues; NR, not reported; OR, odds ratio.

[a] Persistent severe hepatic steatosis.

[b] Severe statosis associated with severe fibrosis.

oxidized LDL levels and increased rates of dyslipidemia (from 33% to 39%) [50]. In addition to this, there were studies showing that TAF may increase the weight of patients. CHB patients were converted from another NA to TAF for 12 months, and their body weight increased significantly ($p < 0.001$), with 21.1% of patients gaining more than 5% weight [51]. Similarly one study showed that CHB patients who switched from TDF to TAF had significantly higher weight and BMI after 72 weeks ($p < 0.01$) [52]. Paradoxically, some studies had shown that patients treated with TAF did not elevated lipids compared to HBV-uninfected controls [53].

In conclusion, many studies have shown that TDF has a lipid-lowering effect, and TAF may cause dyslipidemia and weight gain [54]. Dyslipidemia increases the risk of cardiovascular disease [55,56,57]. Therefore, for CHB patients using NAs, it is important to pay attention not only to the presence of new steatosis and exacerbation of steatosis, but also to blood lipids and body weight to assess the risk of cardiovascular disease.

3. Prognosis of HBV infection combined with NAFLD

Both HBV infection and NAFLD are common chronic liver diseases. The effect of steatosis on fibrosis has attracted attention and therefore many such convenient studies are available (Table 3).

Untreated CHB patients with normal ALT and HBV DNA <2000 IU/ml were followed for 3 years, liver fibrosis was more pronounced in patients with persistent severe hepatic steatosis (OR = 2.38, 95%CI 1.23–4.60) [29]. The results of the Seto et al. study also confirmed a significant correlation between severe steatosis and severe liver fibrosis in CHB patients (21.4% vs. 11.9%, $P < 0.01$) [58]. A study in Taiwan, China, reviewed 104 liver biopsies with a histological diagnosis of NAFLD or cryptogenic cirrhosis, and the incidence of advanced fibrosis was as high as 39.42%, with a significant correlation between liver fibrosis and HBV infection (OR = 3.55, 95%CI 1.46–8.58) [59]. A study in Hong Kong, China also found that 459 HBeAg-negative CHB patients were followed up for 10

Table 4
Effect of hepatic steatosis on the progression of HCC in CHB patients.

Number of patients	Country	Treatment (proportion of treated patients)	Follow-up (years)	Cumulative incidence of HCC with steatosis vs without steatosis	Multivariate Cox analysis for HCC development; HR or OR (95%CI)	Reference
Total:826 Cirrhosis:262 No cirrhosis:564	Korea	NAs (100%)	3.59	NR P = 0.043	1.67(1.05–2.63)	Cho et al. [68]
Total:270 Cirrhosis:74 No cirrhosis: 196	China	NAs or PEG- IFN (89.6%)	6.66	8.4% vs 1.2% P = 0.0043	7.27(1.52–34.76)	Chan et al. [69]
Total:321 Cirrhosis:64 No cirrhosis:257	Korea	AVT (94.1%)	5.3	8.2% vs 1.9% P = 0.004	3.01(1.12–8.05)	Lee et al. [70]
Total: 2158 Cirrhosis:58 No cirrhosis: 2100	US and China	NAs (33.5%)	10.99	3.74% vs 6.18% P = 0.0001	0.21(0.09–0.51)[a] 1.24(0.73–2.12)[b]	Li et al. [28]
Total: 2403 Cirrhosis:371 No cirrhosis: 2032	China	NAs (57.1%)	3.87	2.27% vs 2.88% P = 0.01	0.99(0.99–1.00)[c]	Mak et al. [71]
Total: 2385 Cirrhosis:114 No cirrhosis:2271	China	NAs or IFN (8.2%)	28.10	NR	0.49 (0.36–0.66)	Hsueh et al. [30]
Total:720 Cirrhosis:NR No cirrhosis:NR	Korea	naïve	3	NR	1.04(0.57–1.89)	Chang et al. [32]
Total: 334 Cirrhosis:164 No cirrhosis:170	South Korea	NAs (100%)	3.22	NR P = 0.216	NR P = 0.380[c]	Kim et al. [39]
Total:102 Cirrhosis:36 No cirrhosis:66	Korea	NAs (100%)	3.77	NR P = 0.597	0.57(0.07–4.74) P = 0.602[d]	Lee et al. [72]

Abbreviations: AVT, antiviral therapy; CHB, chronic hepatitis B; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; NAs, nucleos(t)ide analogues; NR, not reported; OR, odds ratio; PEG-IFN, pegylated interferon.

[a] Treated with antiviral treatment.
[b] Untreated with antiviral treatment.
[c] controlled attenuation parameter value.
[d] Univariable analyses.

years, and HS was an independent factor for fibrosis progression (OR = 4.49, 95%CI 1.99–10.10) [60]. Furthermore, some studies have shown that steatohepatitis was an independent preditor of significant fibrosis and advanced fibrosis in patients with CHB (untreated) [61,62]. Overall, most studies demonstrated a correlation between steatosis and fibrosis [63,64,65]. Nevertheless, several studies showed no correlation between steatosis and fibrosis [66,67]. For instance, in a retrospective study in South Korea, treatment-naïve CHB patients with normal ALT and HBV DNA <2000IU/ml were followed up for 3 years and no correlation was found between HS and fibrosis progression (OR = 1.09, 95%CI 0.64–1.85) [32].

Whether metabolic factors combined with virologic factors play a greater role in the progression of liver fibrosis and whether only severe steatosis leads to fibrosis progression requires a large sample of patients with both co-morbidities for long-term follow-up and screening for fibrosis.

The occurrence of HCC in patients with HBV infection combined with NAFLD is also of significant concern (Table 4). Some studies have shown that HS is positively correlated with the occurrence of HCC. In a Korean cohort study of 826 CHB patients (HBV DNA <2000 IU/mL with antiviral treatment) with a median follow-up of 43.1 months, 86 patients developed HCC and NAFLD was significantly associated with the development of HCC (aHR = 1.67, 95%CI 1.05–2.63) [68]. Comparably, a retrospective study in Hong Kong, China included 270 CHB patients followed up for 79.9 months, 11 developed HCC, 9 of whom had combined fatty liver, and multifactorial analysis revealed that fatty liver was an independent influential factor for HCC (HR = 7.27, 95% CI 1.52–34.76) [69]. Intriguingly, 321 CHB patients followed about 5.3 years, coexisting fatty liver (by liver biopsy) was a high risk factor for the development of HCC (aHR = 3.01, 95% CI 1.12–8.05), however after balancing metabolic factors such as obesity, history of hypertension, diabetes, triglyceride, HDL-C and fasting glucose, fatty liver was not significant correlation with HCC(aHR = 1.71, 95% CI 0.40–7.23) [70].

Several additional studies implied that steatosis reduced the incidence of HCC in CHB patients receiving antiviral therapy (HR = 0.21,95% CI 0.09–0.51) [28]. The cumulative incidence of HCC was 2.88%, 1.56% and 0.71% in CHB patients with no HS, mild-to-moderate HS and severe HS, respectively(p = 0.01) in 2403 CHB patients (57.1% receiving antiviral therapy, 46.4 months follow-up) at Queen Mary Hospital, Hong Kong, China [71]. Patients with severe steatosis had a lower risk of developing HCC and a higher cumulative HCC survival rate. The results of another study in Taiwan, China, suggested that HS reduced the risk of HCC (sub-distribution hazard ratio = 0.49,95%CI 0.36–0.66) while the PNPLA3-148 M variant increased the risk of HCC [30].

Still other studies did not find HS associated with the development of HCC in CHB patients. In a retrospective Korean study of 720 treatment-naïve CHB patients with normal ALT and HBV DNA <2000 IU/ml followed for 3 years, HS was not associated with the development of HCC (OR = 1.04,95%CI 0.57–1.89) [32]. Two other Korean studies, in CHB patients receiving NA, likewise did not find a correlation between HS and HCC development [39,72].

Whether HS is a favorable or harmful factor for HCC remains unclear. The factors such as whether receive antiviral therapy and the presence of fibrosis, as well as metabolic and genetic factors that may be involved in the development of HCC and require attention.

4. Conclusions

HBV infection in combination with NAFLD is very common. Most current studies suggest that HBV infection reduces the incidence of NAFLD, which may be related to the negative regulatory role of HBV in lipid metabolism. NAFLD can promote the spontaneous clearance of HBsAg. The intrinsic mechanism may be enhanced T-cell response and TLR4-mediated innate immune response. The effect of steatosis on antiviral efficacy has been reported inconsistently. TDF has a lipid-lowering effect, and TAF may cause dyslipidemia and weight gain. Majority of studies demonstrated steatosis contributes to the progression of liver fibrosis. However, the outcome of HBV infection combined with NAFLD predisposing to the progression of HCC remains controversial.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article. </p>

Funding statement

This work was supported by the Chinese National Natural Science Foundation (81900537), Beijing Hospitals Authority Clinical medicine Development of special funding support (XMLX202125), Capital Health Research and Development Projects (2020-1-2181), Beijing Natural Science Foundation (M22030-7222093), Capital clinical diagnosis and treatment technology research and transformation application project (Z211100002921059), Capital clinical diagnosis and treatment technology research and transformation application project (Z201100005520046).

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

References

[1] M.H. Nguyen, G. Wong, E. Gane, J.H. Kao, G. Dusheiko, Hepatitis B virus: advances in prevention, diagnosis, and therapy, Clin. Microbiol. Rev. 33 (2) (2020) e00046, https://doi.org/10.1128/CMR.00046-19, 19.

[2] J. Liu, W. Liang, W. Jing, M. Liu, Countdown to 2030: eliminating hepatitis B disease, China, Bull. World Health Organ. 97 (3) (2019) 230–238, https://doi.org/10.2471/BLT.18.219469.

[3] M. Nassal, HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B, Gut 64 (12) (2015) 1972–1984, https://doi.org/10.1136/gutjnl-2015-309809.

[4] M.G. Martinez, A. Boyd, E. Combe, B. Testoni, F. Zoulim, Covalently closed circular DNA: the ultimate therapeutic target for curing HBV infections, J. Hepatol. 75 (3) (2021) 706–717, https://doi.org/10.1016/j.jhep.2021.05.013.

[5] S. Tsukuda, K. Watashi, Hepatitis B virus biology and life cycle, Antivir. Res. 182 (2020), 104925, https://doi.org/10.1016/j.antiviral.2020.104925.

[6] Z.M. Younossi, M. Stepanova, Y. Younossi, et al., Epidemiology of chronic liver diseases in the USA in the past three decades, Gut 69 (3) (2020) 564–568, https://doi.org/10.1136/gutjnl-2019-318813.

[7] J.G. Fan, S.U. Kim, V.W.S. Wong, New trends on obesity and NAFLD in Asia, J. Hepatol. 67 (4) (2017) 862–873, https://doi.org/10.1016/j.jhep.2017.06.003.

[8] Z.M. Younossi, A.B. Koenig, D. Abdelatif, Y. Fazel, L. Henry, M. Wymer, Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes: HEPATOLOGY, Vol. XX, No. X 2016, Hepatology 64 (1) (2016) 73–84, https://doi.org/10.1002/hep.28431.

[9] J.M. Paik, P. Golabi, Y. Younossi, A. Mishra, Z.M. Younossi, Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD, Hepatology 72 (5) (2020) 1605–1616, https://doi.org/10.1002/hep.31173.

[10] L. Zhu, J. Jiang, X. Zhai, et al., Hepatitis B virus infection and risk of non-alcoholic fatty liver disease: a population-based cohort study, Liver Int. 39 (1) (2019) 70–80, https://doi.org/10.1111/liv.13933.

[11] M. Khalili, D.E. Kleiner, W.C. King, et al., Hepatic steatosis and steatohepatitis in a large North American cohort of adults with chronic hepatitis B, Am. J. Gastroenterol. 116 (8) (2021) 1686–1697, https://doi.org/10.14309/ajg.0000000000001257.

[12] Q. Zheng, B. Zou, Y. Wu, et al., Systematic review with meta-analysis: prevalence of hepatic steatosis, fibrosis and associated factors in chronic hepatitis B, Aliment. Pharmacol. Ther. 54 (9) (2021) 1100–1109, https://doi.org/10.1111/apt.16595.

[13] E.J. Joo, Y. Chang, J.S. Yeom, S. Ryu, Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: a cohort study, Hepatology 65 (3) (2017) 828–835, https://doi.org/10.1002/hep.28917.

[14] Cheng YL, Wang YJ, Kao WY, et al. Inverse Association between Hepatitis B Virus Infection and Fatty Liver Disease: A Large-Scale Study in Populations Seeking for Check-Up. Wang Y, ed. PLoS ONE. 2013;8(8):e72049. doi:10.1371/journal.pone.0072049.

[15] V.W.S. Wong, G.L.H. Wong, W.C.W. Chu, et al., Hepatitis B virus infection and fatty liver in the general population, J. Hepatol. 56 (3) (2012) 533–540, https://doi.org/10.1016/j.jhep.2011.09.013.

[16] M.W. Yu, C.L. Lin, C.J. Liu, et al., Hepatic steatosis and development of type 2 diabetes: impact of chronic hepatitis B and viral specific factors, *J Formos Med Assoc*. Published online November 8 (21) (2021) S0929–S6646, https://doi.org/10.1016/j.jfma.2021.10.014, 00486-1.

[17] M.M. Wang, G.S. Wang, F. Shen, G.Y. Chen, Q. Pan, J.G. Fan, Hepatic steatosis is highly prevalent in hepatitis B patients and negatively associated with virological factors, Dig. Dis. Sci. 59 (10) (2014) 2571–2579, https://doi.org/10.1007/s10620-014-3180-9.

[18] M. Keikha, A. Sahebkar, T. Jamialahmadi, M. Karbalaei, Metabolic Syndromes, Hepatitis B Virus (HBV), and Hepatitis C Virus as Three Factors Involved in the Development of Hepatic Steatosis: a Systematic Review and Meta-Analysis, 2022. Published online.

[19] W. Jiang, Liu C. hai, D. Wu, Y.J. Wang, H. Tang, Abnormal transaminase and lipid profiles in coexisting diseases in patients with fatty liver: a population study in Sichuan, Biosci. Rep. 41 (12) (2021), BSR20211769, https://doi.org/10.1042/BSR20211769.

[20] E.J. Joo, Y. Chang, J.S. Yeom, Y.K. Cho, S. Ryu, Chronic hepatitis B virus infection and risk of dyslipidaemia: a cohort study, J. Viral Hepat. 26 (1) (2019) 162–169, https://doi.org/10.1111/jvh.13014.

[21] P.T. Liu, A.C. Hwang, J.D. Chen, Combined effects of hepatitis B virus infection and elevated alanine aminotransferase levels on dyslipidemia, Metabolism 62 (2) (2013) 220–225, https://doi.org/10.1016/j.metabol.2012.07.022.

[22] J. Zhang, N. Ling, Y. Lei, M. Peng, P. Hu, M. Chen, Multifaceted interaction between hepatitis B virus infection and lipid metabolism in hepatocytes: a potential target of antiviral therapy for chronic hepatitis B, Front. Microbiol. 12 (2021), 636897, https://doi.org/10.3389/fmicb.2021.636897.

[23] Y. Wu, X e li Peng, Y bing Zhu, Yan X. li, Chen W. nan, X. Lin, Hepatitis B virus X protein induces hepatic steatosis by enhancing the expression of liver fatty acid binding protein. Sandri-goldin RM, J. Virol. 90 (4) (2016) 1729–1740, https://doi.org/10.1128/JVI.02604-15.

[24] K.H. Kim, H. Shin, K. Kim, et al., Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARγ, Gastroenterology 132 (5) (2007) 1955–1967, https://doi.org/10.1053/j.gastro.2007.03.039.

[25] J.Y. Kim, E.H. Song, H.J. Lee, et al., HBx-induced hepatic steatosis and apoptosis are regulated by TNFR1- and NF-κB-Dependent pathways, J. Mol. Biol. 397 (4) (2010) 917–931, https://doi.org/10.1016/j.jmb.2010.02.016.

[26] C.M. Chu, D.Y. Lin, Y.F. Liaw, Does increased body mass index with hepatic steatosis contribute to seroclearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? Int. J. Obes. 31 (5) (2007) 871–875, https://doi.org/10.1038/sj.ijo.0803479.

[27] C.M. Chu, D.Y. Lin, Y.F. Liaw, Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without, Dig. Dis. Sci. 58 (1) (2013) 275–281, https://doi.org/10.1007/s10620-012-2343-9.

[28] J. Li, H.I. Yang, M.L. Yeh, et al., Association between fatty liver and cirrhosis, hepatocellular carcinoma, and hepatitis B surface antigen seroclearance in chronic hepatitis B, J. Infect. Dis. 224 (2) (2021) 294–302, https://doi.org/10.1093/infdis/jiaa739.

[29] L.Y. Mak, R.W.H. Hui, J. Fung, et al., Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B, J. Hepatol. 73 (4) (2020) 800–806, https://doi.org/10.1016/j.jhep.2020.05.040.

[30] R.C. Hsueh, W.J. Wu, C.L. Lin, et al., Impact of PNPLA3 p.I148M and hepatic steatosis on long-term outcomes for hepatocellular carcinoma and HBsAg seroclearance in chronic hepatitis B, JHC ume 9 (2022) 301–313, https://doi.org/10.2147/JHC.S355540.

[31] F. Bacaksız, H. Gökcan, M. Akdoğan, et al., Role of hepatosteatosis in HBsAg seroconversion in HBeAg-negative chronic hepatitis B patients, Int. J. Clin. Pract. 75 (12) (2021), https://doi.org/10.1111/ijcp.14899.

[32] J.W. Chang, J.S. Lee, H.W. Lee, et al., No influence of hepatic steatosis on the 3-year outcomes of patients with quiescent chronic hepatitis B, J. Viral Hepat. 28 (11) (2021) 1545–1553, https://doi.org/10.1111/jvh.13594.

[33] D. Hu, H. Wang, H. Wang, et al., Non-alcoholic hepatic steatosis attenuates hepatitis B virus replication in an HBV-immunocompetent mouse model, Hepatol Int 12 (5) (2018) 438–446, https://doi.org/10.1007/s12072-018-9877-7.

[34] Z. Zhang, Q. Pan, X.Y. Duan, et al., Fatty liver reduces hepatitis B virus replication in a genotype B hepatitis B virus transgenic mice model: steatosis reduces Hepatitis B virus replication, J. Gastroenterol. Hepatol. 27 (12) (2012) 1858–1864, https://doi.org/10.1111/j.1440-1746.2012.07268.x.

[35] L. Lu, Y.L. Liu, W.J. Yang, et al., [Model building-up and observation on the mouse carried chronic hepatitis B and nonalcoholic fatty liver disease], Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 27 (5) (2013) 332–335.

[36] N. Patel, D. Boghici, M. Rava, et al., Enhanced T cell responses in patients and mouse model of hepatitis B and comorbid non-alcoholic fatty liver disease, J. Hepatol. 77 (2022) S259–S260, https://doi.org/10.1016/S0168-8278(22)00890-X.

[37] R.N. Zhang, Q. Pan, Z. Zhang, H.X. Cao, F. Shen, J.G. Fan, 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. 15 (5) (2015), https://doi.org/10.5812/hepatmon.15(5)2015.27909.

[38] X. Jin, Chen Y. peng, Y da Yang, Y. Li, L. ming Zheng, Xu C. qing, Association between hepatic steatosis and entecavir treatment failure in Chinese patients with chronic hepatitis B. Jhaveri R, PLoS One 7 (3) (2012), e34198, https://doi.org/10.1371/journal.pone.0034198.

[39] D.S. Kim, M.Y. Jeon, H.W. Lee, et al., Influence of hepatic steatosis on the outcomes of patients with chronic hepatitis B treated with entecavir and tenofovir, Clin. Mol. Hepatol. 25 (3) (2019) 283–293, https://doi.org/10.3350/cmh.2018.0054.

[40] S.H. Kim, E.J. Cho, B. Jang, et al., Comparison of biochemical response during antiviral treatment in patients with chronic hepatitis B infection, Liver Int. 42 (2) (2022) 320–329, https://doi.org/10.1111/liv.15086.
[41] L. Gong, J. Liu, J. Wang, G.Q. Lou, J.P. Shi, Hepatic steatosis as a predictive factor of antiviral effect of pegylated interferon therapy in patients with hepatitis B, Transplant. Proc. 47 (10) (2015) 2886–2891, https://doi.org/10.1016/j.transproceed.2015.10.023.
[42] Y.C. Hsu, M.L. Yeh, G.L.H. Wong, et al., Incidences and determinants of functional cure during entecavir or tenofovir disoproxil fumarate for chronic hepatitis B, J. Infect. Dis. 224 (11) (2021) 1890–1899, https://doi.org/10.1093/infdis/jiab241.
[43] J. Li, A.K. Le, K.T. Chaung, et al., Fatty liver is not independently associated with the rates of complete response to oral antiviral therapy in chronic hepatitis B patients, Liver Int. 40 (5) (2020) 1052–1061, https://doi.org/10.1111/liv.14415.
[44] B. Ceylan, F. Arslan, A. Batirel, et al., Impact of fatty liver on hepatitis B virus replication and virologic response to tenofovir and entecavir, Turk. J. Gastroenterol. 27 (1) (2016) 42–46, https://doi.org/10.5152/tjg.2015.150348.
[45] M. Cindoruk, T. Karakan, S. Unal, Hepatic steatosis has no impact on the outcome of treatment in patients with chronic hepatitis B infection, J. Clin. Gastroenterol. 41 (5) (2007) 513–517, https://doi.org/10.1097/01.mcg.0000225586.78330.60.
[46] Y.C. Chen, W.J. Jeng, C.W. Hsu, C.Y. Lin, Impact of hepatic steatosis on treatment response in nucleos(t)ide analogue-treated HBeAg-positive chronic hepatitis B: a retrospective study, BMC Gastroenterol. 20 (1) (2020) 146, https://doi.org/10.1186/s12876-020-01289-w.
[47] J. Yao, L. Zhou, X. Hua, M. Kong, Y. Chen, Z. Duan, Effects of nucleos(t)ide analogs on body composition in HBV-infected men: an age- and BMI-matched, cross-sectional study, Nutrition 32 (11–12) (2016) 1206–1210, https://doi.org/10.1016/j.nut.2016.04.001.
[48] A.A. Shaheen, M. AlMattooq, S. Yazdanfar, et al., Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers, Aliment. Pharmacol. Ther. 46 (6) (2017) 599–604, https://doi.org/10.1111/apt.14218.
[49] J. Lim, W. Choi, J.H. Shim, et al., Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in treatment-naïve chronic hepatitis B, Liver Int. (2022), https://doi.org/10.1111/liv.15261. Published online April 3, 2022:liv.15261.
[50] K. Suzuki, G. Suda, Y. Yamamoto, et al., Effect of switching from tenofovir disoproxil fumarate to tenofovir alafenamide on lipid profiles in patients with hepatitis B. Chemin I, PLoS One 17 (1) (2022), e0261760, https://doi.org/10.1371/journal.pone.0261760.
[51] M.L. Yeh, P.C. Liang, S. Trinh, et al., Body weight changes in treated hepatitis B patients switching to tenofovir alafenamide, J. Formos. Med. Assoc. (2021), https://doi.org/10.1016/j.jfma.2021.09.009. Published online October 2021:S0929664621004319.
[52] B.T. Lee, M. Chang, C. Lim, H.S. Bae, T. Fong, Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients, JGH Open 5 (2) (2021) 258–263, https://doi.org/10.1002/jgh3.12481.
[53] J. Jeong, J.W. Shin, S.W. Jung, E.J. Park, N.H. Park, Tenofovir alafenamide treatment may not worsen the lipid profile of chronic hepatitis B patients: a propensity score-matched analysis, Clin. Mol. Hepatol. 28 (2) (2022) 254–264, https://doi.org/10.3350/cmh.2021.0314.
[54] K.S. Byun, J. Choi, J.H. Kim, et al., Tenofovir alafenamide for drug-resistant hepatitis B: a randomized trial for switching from tenofovir disoproxil fumarate, Clin. Gastroenterol. Hepatol. 20 (2) (2022) 427–437.e5, https://doi.org/10.1016/j.cgh.2021.04.045.
[55] K.K. Teo, T. Rafiq, Cardiovascular risk factors and prevention: a perspective from developing countries, Can. J. Cardiol. 37 (5) (2021) 733–743, https://doi.org/10.1016/j.cjca.2021.02.009.
[56] F. Gomez-Delgado, N. Katsiki, J. Lopez-Miranda, P. Perez-Martinez, Dietary habits, lipoprotein metabolism and cardiovascular disease: from individual foods to dietary patterns, Crit. Rev. Food Sci. Nutr. 61 (10) (2021) 1651–1669, https://doi.org/10.1080/10408398.2020.1764487.
[57] P.S. Jellinger, Y. Handelsman, P.D. Rosenblit, et al., American association of clinical endocrinologists and American college of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease, Endocr. Pract. 23 (2017) 1–87, https://doi.org/10.4158/EP171764 (APPGL).
[58] W.K. Seto, R.W.H. Hui, L.Y. Mak, et al., Association between hepatic steatosis, measured by controlled attenuation parameter, and fibrosis burden in chronic hepatitis B, Clin. Gastroenterol. Hepatol. 16 (4) (2018) 575–583.e2, https://doi.org/10.1016/j.cgh.2017.09.044.
[59] H.J. Su, J.H. Kao, T.C. Tseng, et al., Pathologic findings of patients with nonalcoholic fatty liver disease and the impact of concurrent hepatitis B virus infection in Taiwan, J. Formos. Med. Assoc. 119 (10) (2020) 1476–1482, https://doi.org/10.1016/j.jfma.2020.05.027.
[60] L. Mak, W. Seto, R.W. Hui, et al., Fibrosis evolution in chronic hepatitis B e antigen-negative patients across a 10-year interval, J. Viral Hepat. 26 (7) (2019) 818–827, https://doi.org/10.1111/jvh.13095.
[61] Y. Huang, Q. Gan, R. Lai, et al., Application of fatty liver inhibition of progression algorithm and steatosis, activity, and fibrosis score to assess the impact of non-alcoholic fatty liver on untreated chronic hepatitis B patients, Front. Cell. Infect. Microbiol. 11 (2021), 733348, https://doi.org/10.3389/fcimb.2021.733348.
[62] P. Charatcharoenwitthaya, A. Pongpaibul, U. Kaosombatwattana, et al., The prevalence of steatohepatitis in chronic hepatitis B patients and its impact on disease severity and treatment response, Liver Int. 37 (4) (2017) 542–551, https://doi.org/10.1111/liv.13271.
[63] S. Wong, W. Chan, R. Mohamed, Fatty liver is associated with advanced fibrosis but does not predict adverse outcomes in patients with chronic hepatitis B, J. Viral Hepat. 27 (12) (2020) 1297–1305, https://doi.org/10.1111/jvh.13361.
[64] Z. Karacaer, G. Okur, H. Cermik, D. Altun, Is there an influence of hepatic steatosis on fibrosis and necroinflammation in young patients with chronic viral hepatitis B? PGM (Postgrad. Med.) 128 (7) (2016) 697–700, https://doi.org/10.1080/00325481.2016.1221733.
[65] R.W.H. Hui, W.K. Seto, K.S. Cheung, et al., Inverse relationship between hepatic steatosis and hepatitis B viremia: results of a large case-control study, J. Viral Hepat. 25 (1) (2018) 97–104, https://doi.org/10.1111/jvh.12766.
[66] J.W. Yun, Y.K. Cho, J.H. Park, et al., Hepatic steatosis and fibrosis in young men with treatment-naïve chronic hepatitis B, Liver Int. 29 (6) (2009) 878–883, https://doi.org/10.1111/j.1478-3231.2009.01976.x.
[67] R. Pais, E. Rusu, D. Zilisteanu, et al., Prevalence of steatosis and insulin resistance in patients with chronic hepatitis B compared with chronic hepatitis C and non-alcoholic fatty liver disease, Eur. J. Intern. Med. 26 (1) (2015) 30–36, https://doi.org/10.1016/j.ejim.2014.12.001.
[68] H. Cho, Y. Chang, J.H. Lee, et al., Radiologic nonalcoholic fatty liver disease increases the risk of hepatocellular carcinoma in patients with suppressed chronic hepatitis B, J. Clin. Gastroenterol. 54 (7) (2020) 633–641, https://doi.org/10.1097/MCG.0000000000001217.
[69] A.W.H. Chan, G.L.H. Wong, H.Y. Chan, et al., Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B: steatosis and cancer in hepatitis B, J. Gastroenterol. Hepatol. 32 (3) (2017) 667–676, https://doi.org/10.1111/jgh.13536.
[70] Y.B. Lee, Y. Ha, Y.E. Chon, et al., Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B, Clin. Mol. Hepatol. 25 (1) (2019) 52–64, https://doi.org/10.3350/cmh.2018.0040.
[71] L.Y. Mak, R.W.H. Hui, J. Fung, et al., Reduced hepatic steatosis is associated with higher risk of hepatocellular carcinoma in chronic hepatitis B infection, Hepatol Int 15 (4) (2021) 901–911, https://doi.org/10.1007/s12072-021-10218-2.
[72] J. Lee, S.H. Yoo, W. Sohn, et al., Obesity and hepatocellular carcinoma in patients receiving entecavir for chronic hepatitis B, Clin. Mol. Hepatol. 22 (3) (2016) 339–349, https://doi.org/10.3350/cmh.2016.0021.