Original Article

Concurrence and impact of hepatic steatosis on chronic hepatitis B patients: a systematic review and meta-analysis

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Background: The association between hepatic steatosis (HS) and chronic hepatitis B (CHB) remains controversial. We performed a systematic review and meta-analysis to investigate the latest concurrence rate and impact of HS on CHB patients.

Methods: Relevant studies were identified by searching PubMed, EMBASE, and the Cochrane Library from January 1, 2000 to December 2, 2020. We calculated the pooled prevalence of HS in CHB patients using a random effects model. A subgroup analysis was performed to explore the impact of HS on CHB patients. This study is registered with PROSPERO (No. CRD42021242584).

Results: A total of 98 studies with a population of 48,472 patients were included. The global prevalence of HS in CHB patients was 34.93% [95% confidence interval (CI): 32.01–37.90%]. Overweight status, hypertension, diabetes, hyperlipidemia, and metabolic syndrome showed a higher risk for developing HS in CHB patients, while positive hepatitis B e antigen (HBeAg) status was negatively associated with the presence of HS [odds ratio (OR) =0.81, 95% CI: 0.70–0.93]. The pooled analysis showed no significant association between HS and fibrosis progression (OR =0.68, 95% CI: 0.44–1.05). However, the coexistence of HS was negatively associated with the antiviral therapy response in CHB patients, including virological response (OR =0.69, 95% CI: 0.48–0.99) and alanine aminotransferase (ALT) normalization (OR =0.44, 95% CI: 0.28–0.69).

Discussion: The global prevalence of HS in CHB patients is higher than previously estimated. The concurrence of HS could impact the replication of HBV and the effectiveness of antiviral therapy in CHB patients. However, coexistence with HS did not show a higher risk of developing advanced fibrosis in CHB patients.

Keywords: Hepatic steatosis (HS); chronic hepatitis B (CHB); concurrence; influence factors; meta-analysis

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Introduction

Hepatitis B virus (HBV) infection is a significant cause of cirrhosis, hepatocellular carcinoma (HCC), grave morbidity, and mortality (1). Globally, it is estimated that 240 to 350 million of the world's population has hepatitis B (2). Nonalcoholic fatty liver disease (NAFLD) is another one of the most common chronic liver diseases worldwide (3). Accompanied by the rapid increase in the burden of NAFLD, the concurrence of NAFLD and HBV infection has increased (4). However, the prevalence varies between studies, ranging from 14% to 70% (5). It is estimated that 25–30% of chronic hepatitis B (CHB) patients have concomitant hepatic steatosis (HS) (5,6).

A previous review reported that hepatitis C virus (HCV) could directly impact hepatic lipid metabolism, which leads to triglyceride accumulation (7), while another study found HS to be more frequent and severe in genotype 3 infection (8). However, the nature of the interaction between CHB and HS remains elusive, which is of interest to many researchers (9). For example, recent studies have indicated that the coexistence of HS and CHB is associated with an increased risk of fibrosis progression and hepatic and extrahepatic malignancies (10-12). The concurrence of these 2 common liver diseases shows deteriorating effects that aggravate liver injury and disease progression. The impact of HS on CHB is not consistent. An early study reported that HS was not correlated with the degree of fibrosis in patients with CHB. Furthermore, HS in CHB patients was associated with changes in anthropometric indices and metabolic factors but not HBV (13). Other research has shown that HS does not affect the virological response to antiviral treatment in CHB patients (14,15). However, one study reported that metabolic syndrome accounting for HS was an independent risk factor for liver impairment in CHB patients (9).

We thus conducted a systematic review and meta-analysis to provide a comprehensive overview of the epidemiology and impact of HS in CHB patients. We also analyzed the data on the impact of HS on the response to antiviral therapy in patients with CHB. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3052).

Methods

Data sources and search strategy

This study was performed following the PRISMA guidelines (16) and registered with PROSPERO (No. CRD42021242584). For this systematic review and meta-analysis, we systematically searched 3 predominantly English language databases (PubMed, EMBASE, and the Cochrane Library) published between January 1, 2000 and December 2, 2020 for original peer-reviewed articles using the search terms "fatty liver", "non-alcoholic fatty liver disease", and "hepatitis B". The details regarding the search strategy are provided in Supplementary file (Appendix 1).

Eligibility criteria and quality assessment

There were no language restrictions on the search results. The inclusion criteria for the meta-analysis were as follows: (I) an original study with patients diagnosed with CHB; (II) a study defining clear diagnostic tools or criteria for HS; and (III) inclusion of raw and sufficient data to describe the epidemiology, risk factors, or the effectiveness of antiviral therapy (e.g., body indexes and laboratory findings) of CHB patients with and without HS. The exclusion criteria were as follows: (I) a study not identifying patients with CHB; (II) a review article, case report, or abstract, or an article with full-text unavailable; (III) a study not excluding other causes of liver disease, including drug-induced liver disease, autoimmune liver disease, alcoholic fatty liver (or excess alcohol consumption), and other viral hepatitis infection; and (IV) a study unable to provide sufficient information for data extraction. Diagnoses based on biopsy, controlled attenuation parameter (CAP) score, or ultrasound were placed in subgroups and are presented in Table S1. All the included studies were reviewed and evaluated by 2 independent investigators. The articles and citations were managed in EndNote (version X9, Clarivate Analytics).

Statistical analysis

The estimates of HS prevalence in CHB patients were transformed using Freeman-Tukey double arcsine transformation (17). We pooled the study data using random effects models due to the predicted high heterogeneity (18). The combined pooled estimates and their 95% confidence intervals (CIs) were back-transformed to proportions and plotted. The weighted mean difference (WMD) and its 95% CI was calculated to estimate statistical differences of the continuous variables in the simple CHB group and the CHB with HS group, while the odds ratio (OR) and its 95% CI was calculated to estimate whether the categorical variables increased the risk of HS in the

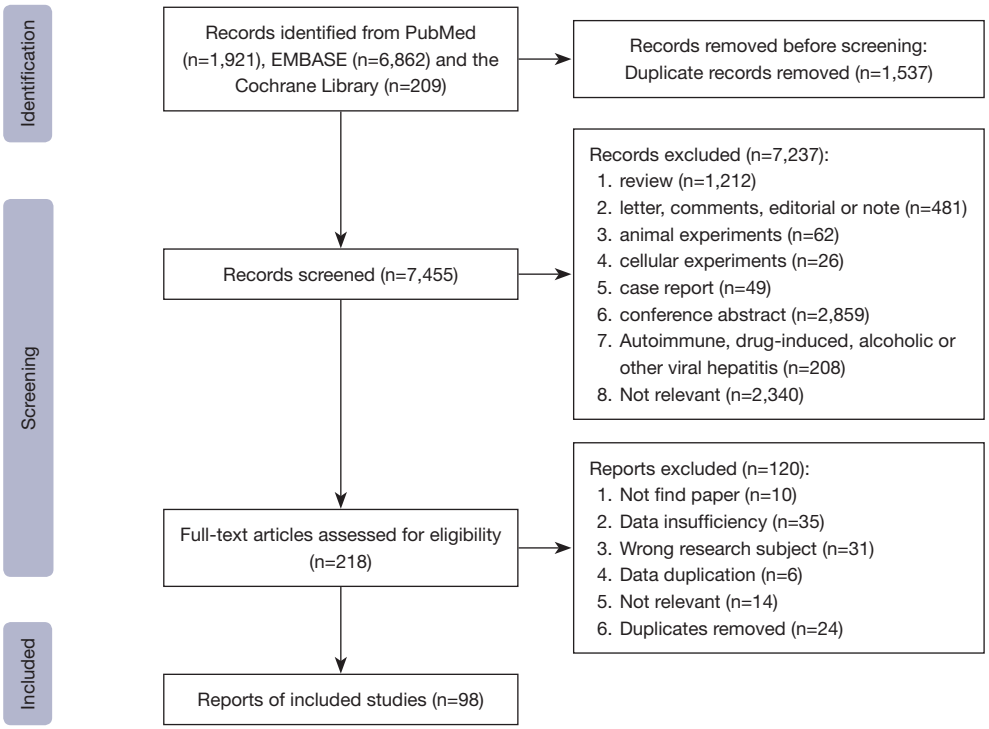

Figure 1 The study selection process for this meta-analysis.

CHB patients. The I^2 statistic was calculated to assess the heterogeneity (19). Egger's test and funnel plots of the HS prevalence in CHB patients after transformation against the standard error were used to assess publication bias (20). We performed a subgroup analysis to estimate the prevalence of HS in CHB patients stratified by country, the year of publication, economic status, World Health Organization (WHO) region, sample size, male sex, diagnostic tools, and diagnostic criteria. We also estimated the impact of HS on the replication of HBV, the progression of fibrosis, and the effectiveness of antiviral therapy in CHB patients. Sensitivity analysis was conducted to evaluate the impact of each study on the overall pooled estimate. The meta-analyses were conducted using R version 3.2.3 (The R Foundation for Statistical Computing) with the meta and metafor packages.

Results

Search results

We identified 8,992 articles, of which 1,537 were duplicates. After the exclusion of duplicates, the titles and abstracts of 7,455 published studies were screened. A total of 218 articles were potentially eligible and screened by a reading of the full text. Of these, 48,472 participants from 98 studies across 20 countries were included in this systematic review and meta-analysis (*Figure 1*). The characteristics of the included studies are summarized in Table S2.

Prevalence of HS in CHB patients

The prevalence rates of different countries are shown in *Figure 2*, and the overall worldwide prevalence of HS in CHB patients was estimated to be 34.93% (95% CI: 32.01–37.90%; *Figure 2*). Concomitant HS with CHB appeared to be more prevalent in high–income countries (36.91%, 95% CI: 33.04–40.87%) compared with middle–income countries (33.93%, 95% CI: 30.22–37.75%). The prevalence of HS in CHB patients diagnosed by liver biopsy was 34.64% (95% CI: 30.74–38.65%), which is the closest to the overall prevalence. However, the prevalence of HS in CHB patients diagnosed by ultrasound (27.40%; 95% CI: 23.79–31.17%) was lower, and that diagnosed by the CAP score (49.15%; 95% CI: 43.80–54.51%) was higher (*Figure 3*). We addressed the heterogeneity associated with the diagnostic criteria of HS by performing a subgroup analysis in Table S1.

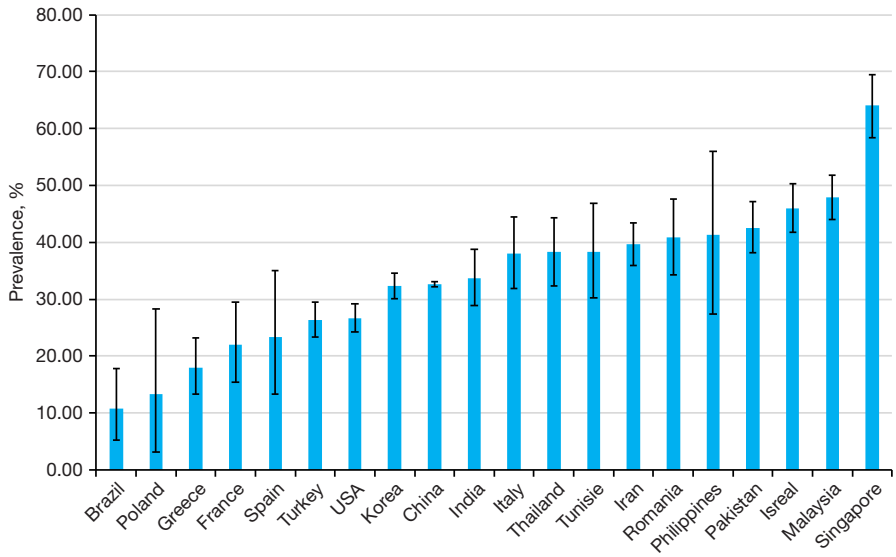

Figure 2 The pooled overall nationwide prevalence of HS in CHB patients. HS, hepatic steatosis; CHB, chronic hepatitis B.

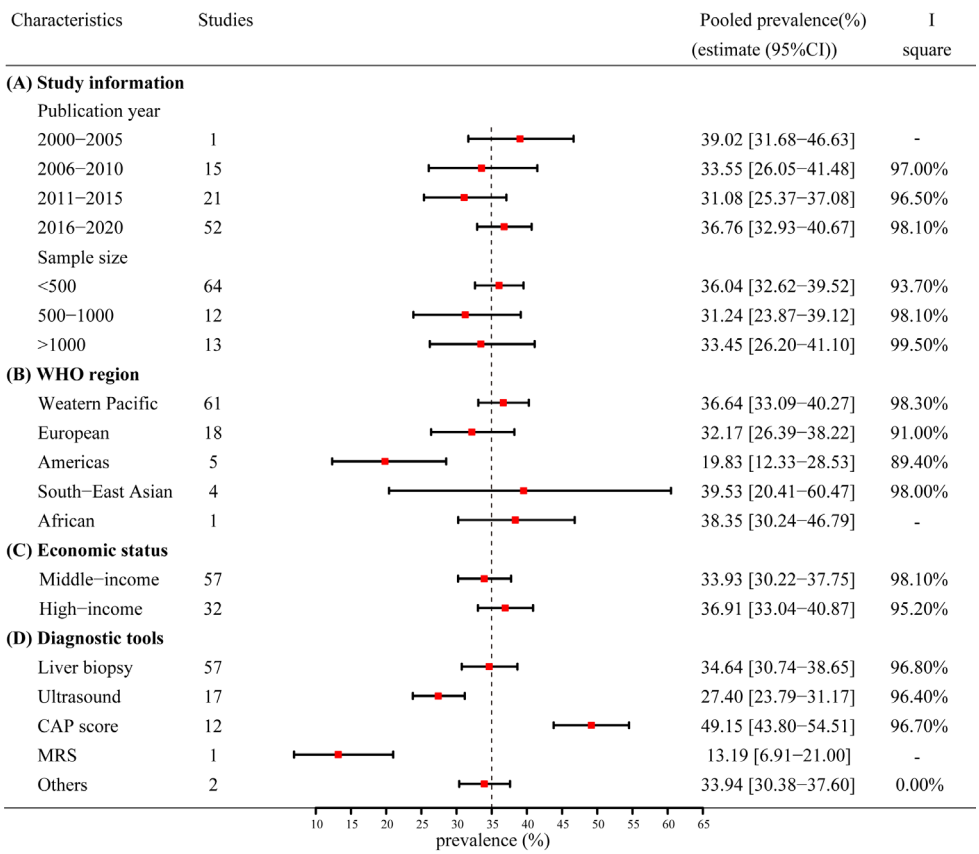

Figure 3 The forest plots of the meta-analysis on demographic and diagnostic features. CI, confidence interval; WHO, World Health Organization; CAP, controlled attenuation parameter; MRS, magnetic resonance spectroscopy.

Table 1 Factors associated with HS in CHB patients

Characteristics	Studies	Pooled OR or WMD, estimate (95% CI)	I^2 (%)	P value
Age	60	2.11* (1.41–2.81)	86.30	<0.0001
Male	59	1.57# (1.37–1.80)	78.10	<0.0001
BMI	44	3.26* (2.72–3.81)	96.60	<0.0001
Overweight	15	4.67# (3.43–6.35)	65.30	<0.0001
Hypertension	17	1.99# (1.69–2.34)	52.90	<0.0001
Diabetes	21	2.48# (1.96–3.13)	69.20	<0.0001
Hyperlipidemia	9	2.68# (1.99–3.61)	74.30	<0.0001
Metabolic syndrome	6	4.02# (2.46–6.57)	77.30	<0.0001
Triglycerides	16	34.91* (25.65–44.17)	85.00	<0.0001
Total cholesterol	16	17.70* (10.79–24.62)	88.90	<0.0001
ALT	22	0.71* (–3.84 to 5.26)	87.00	0.7600
AST	16	–3.44* (–8.38 to 1.50)	93.90	0.1719
HBeAg positive	34	0.81# (0.70–0.93)	56.50	0.0032

*, WMD; #, OR. HS, hepatic steatosis; CHB, chronic hepatitis B; BMI, body mass index; OR, odds ratio; WMD, weighted mean difference; ALT, alanine transaminase; AST, aspartate aminotransferase.

Demographic characteristics and factors associated with HS in CHB patients

Compared to the CHB group, the CHB with HS group was significantly older (WMD =2.11; 95% CI: 1.41–2.80), and males showed a higher risk of developing fatty liver than did females (OR =1.57, 95% CI: 1.37–1.80). Overweight status (OR =4.67, 95% CI: 3.43–6.35), hypertension (OR =1.99, 95% CI: 1.69–2.33), diabetes (OR =2.47, 95% CI: 1.96–3.12), hyperlipidemia (OR =2.68, 95% CI: 1.99–3.61), and metabolic syndrome (OR =4.02, 95% CI: 2.46–6.57) were strong risk factors for the presence of HS in CHB patients. Both serum triglycerides (WMD =34.91, 95% CI: 25.65–44.17) and serum total cholesterol (WMD =17.7, 95% CI: 10.78–24.61) were higher in the CHB with HS group. Compared with the CHB group, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were not significantly different from the CHB with HS group. Hepatitis B e antigen (HBeAg)–positive status showed a lower risk of developing HS in CHB patients (OR =0.81, 95% CI: 0.70–0.93; *Table 1*). We further analyzed the relationship between HBV viral load and the presence of HS in CHB patients. However, the result also showed no significance (Table S3).

Liver fibrosis in concomitant CHB and HS and the potential relationship between HS and antiviral treatment

F2–F4 fibrosis (defined as advanced fibrosis) had no significant relationship with the presence of HS in CHB patients (OR =0.68, 95% CI: 0.44–1.05). Moreover, there was no significant difference in the presence of cirrhosis among CHB patients with or without HS (OR =1.12, 95% CI: 0.75–1.65; *Figure 4*). The outcomes (F2–F4 fibrosis and cirrhosis) had no significant relationship with the presence of HS in CHB patients under different diagnostic modes (Table S4). Our results also showed that CHB with HS had a lower rate of virological response (OR =0.69, 95% CI: 0.48–0.99) and ALT normalization (OR =0.44, 95% CI: 0.28–0.69) than did the simple HBV group after 48 weeks of antiviral therapy.

Publication bias and sensitivity analysis

The shapes of the funnel plots were relatively symmetrical (Figure S1). Egger's test was also conducted and yielded a P value of 0.16 (P>0.05), thus indicating no obvious publication bias. The results of the sensitivity analysis showed that the meta-analysis was stable, and no single

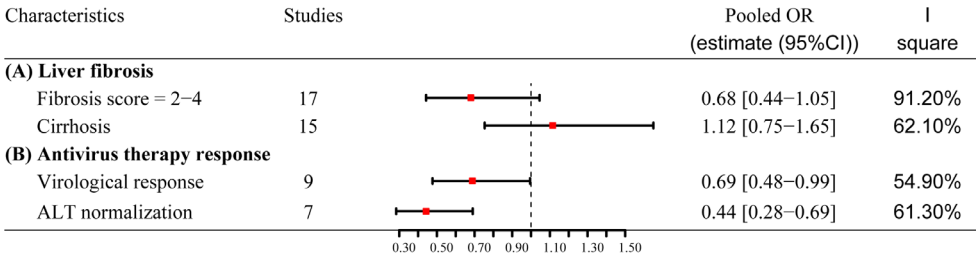

Figure 4 The forest plots of the meta-analysis on the impact of HS on fibrosis progression and the effectiveness of antiviral therapy in CHB patients. CI, confidence interval; ALT, alanine transaminase; OR, odds ratio.

study altered the pooled proportion estimates (Figure S2).

Discussion

This meta-analysis and systematic review included 48,472 participants from 98 studies between January 1, 2000 and December 2, 2020 and provided a comprehensive overview of the prevalence, risk factors, and progression of HS in CHB patients. The worldwide prevalence of HS in CHB patients is currently estimated to be 34.93%, which is higher than previously estimated (5).

In this study, we found a higher prevalence of HS in CHB patients in high-income countries than in middle-income countries, which was similar to the prevalence of HS in the general population. The socioeconomic drivers for these patterns remain to be further investigated (21). In CHB patients, male gender was a strong risk factor for HS in CHB patients (OR =1.64), which is consistent with the general population (5,21,22). Predictably, age showed a positive relationship with fatty liver in CHB patients. This can be explained by the fact that the prevalence of metabolic syndrome increases markedly with aging (23). A previous study indicated that fatty liver in CHB patients is associated with metabolic factors more than it is by viral factors (24). The data in another study provided convincing evidence that an independent inverse relationship does exist between HS and HBV viral load after multivariate analysis was applied (9). This discrepancy may reflect the complexity of concomitant HBV infection and fatty liver in clinical practice. Our pooled analysis demonstrated that metabolic factors had the most important association with the presence of HS in CHB patients. Overweight status, hypertension, diabetes, hyperlipidemia, and metabolic syndrome conferred a 2- to 5-fold increased risk of HS in the liver. However, from the HBV perspective, positive HBeAg status appeared to have a negative association with the presence of HS in CHB patients. HS has been proposed to directly affect HBV-related antigen expression and viral replication in a mouse model (25,26) or to indirectly decrease replication by inducing hepatocyte apoptosis (27). We hypothesize that HS in CHB patients may be mainly due to metabolic factors that indirectly impact the expression of viral markers. Although our pooled data exhibit a seemingly negative relationship between the presence of HS and HBV viral replication in CHB patients, the potential influence of confounding bias in studies should also be considered, and the reported conclusion needs further basic research for verification.

It is important to recognize the probability that the coexistence of HS may accelerate the progression of liver disease (21). In our meta-analysis, the presence of biopsy-proven advanced fibrosis was not influenced by the presence of HS, which was consistent with our finding of a lack of relationship between the presence of HS and the progression of liver function impairment (ALT and AST). Liver fibrosis and consequent cirrhosis are universally recognized as a prelude to HCC (4). Three cohort studies have indicated that concurrent fatty liver increases the risk of HCC among CHB patients (10,12,28). Another retrospective cohort study reported no association between HS and HCC risk after adjustment for metabolic factors in CHB patients (29). However, another study found simple HS to be an independent risk factor for liver cirrhosis and HCC since HS-related lipotoxicity can be lethal for hepatocytes and trigger disease progression (30). Due to the limited studies (n=5) with cases of liver cancer between the 2 groups, as well as the incomplete data and the complicated confounding factors, we cannot draw a straightforward conclusion from the meta-analysis. We hope that more large-scale prospective and the cohort studies with confounders controlled will be conducted to further establish the aggravated risk of HCC in patients

with coexisting HS and CHB. Also, CHB patients with HS need to be closely monitored.

The pooled analysis showed that antiviral therapy for CHB patients was influenced by the presence of fatty liver after 48 weeks of treatment. Previous studies indicated that decreased bioavailability of intrahepatic metabolites of nucleoside analogs (NAs) due to hepatocellular fat droplet accumulation accounted for the different treatment response to NAs therapy (15,31). Moreover, HS coexistence with decreased activity of hepatic cytochrome P450, insulin resistance, and obesity, leading to hepatocellular immune dysfunction, may also affect the treatment outcomes (32,33). Lipid accumulation in hepatocytes also reduces the effective contact between hepatocytes and the drug. Thorough screening and management of HS is needed to improve the long-term therapeutic outcomes of patients chronically infected with HBV. Both CHB and HS can cause chronic liver inflammation, which manifests as elevated ALT levels. However, ALT abnormalities are often misdiagnosed as HBV activation by doctors, leading to premature antiviral therapy, which may be another reason for the poor response to antiviral therapy in CHB patients with HS. Considering the potential negative impact of HS on antiviral therapy, it is necessary to strengthen screening and management, and to implement appropriate measures to control metabolic disorders such as obesity and diabetes.

This study has several strengths. This is the most up-to-date meta-analysis to examine the epidemiology, risk factors, and impact of HS on CHB patients globally from 2000 to 2020. We also estimated the prevalence of HS in CHB patients using sex-specific, country-specific, and diagnostic tool–specific analyses, which could be useful for policy makers. Moreover, we included longitudinal studies that evaluated the association between fatty liver and antiviral therapy for CHB patients, and the duration of the medication and the observational indicators were consistent. Our study also has a number of limitations. First is the high heterogeneity among the included studies. We applied a random effects model and subgroup analysis to evaluate the factors influencing the heterogeneity. Second, most studies included in this meta-analysis originated from Asia, but estimates were applied to all regions. However, China is the major battlefield in the war against the pandemic of HBV infection and NAFLD (21,34). It is suggested that there should be ongoing research in the western world due to the high prevalence of obesity and NAFLD. Third, different diagnostic tools for HS have their advantages and limitations (21). The CAP score might be more accurate for detecting HS than is ultrasound in patients with CHB; however, further studies are needed to reduce the overestimation rates (35). Fourth, the antiviral therapies (NA or pegylated interferon alpha) were not homogeneous in the included studies investigating the influence of HS on antiviral treatment. We hope that more large-scale and prospective cohorts with confounders controlled will be conducted to further establish the influence of HS on antiviral therapy.

Conclusions

In this meta-analysis, HS in CHB patients was estimated to be present in one-third of the population of CHB patients, which is similar to the general population but higher than previously estimated. CHB patients with HS were older than the simple HBV group. Male gender and metabolic factors showed a higher risk for developing HS in CHB patients, while positive HBeAg status was negatively associated with the presence of HS in CHB patients. Although the meta-analysis showed no significant association between fibrosis progression and the presence of HS in CHB patients, the influence of hepatocellular lipid accumulation on antiviral therapy alarmed clinicians, which warrants further investigation. We need a better understanding of the interaction between CHB and HS to design and implement effective anti-HBV therapies and metabolic regulation.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-3052). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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