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

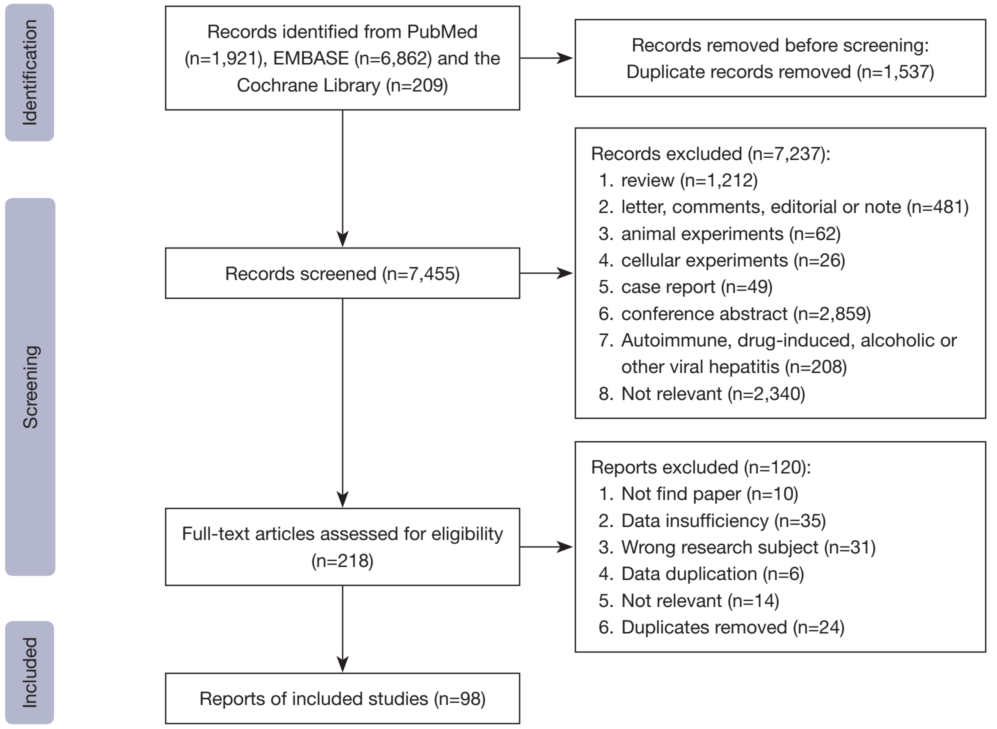

Figure 1 The study selection process for this meta-analysis.

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.

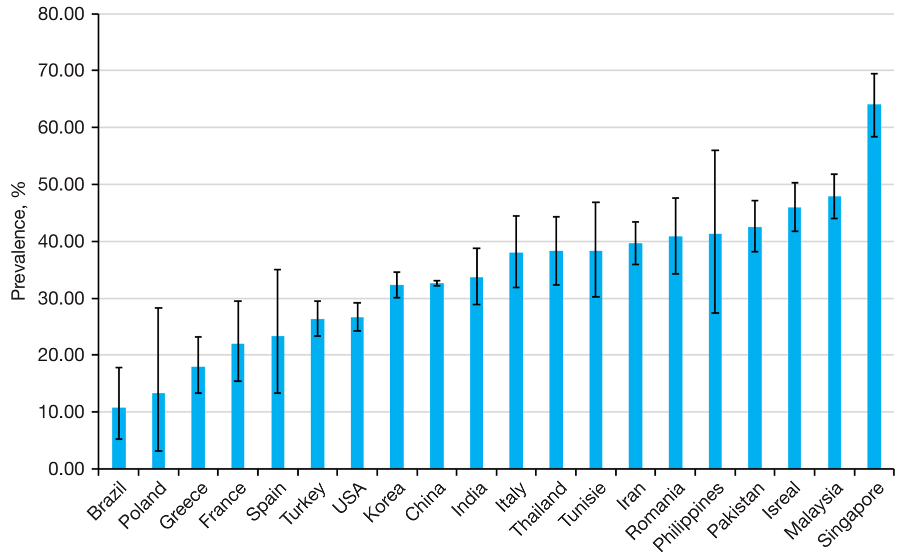

Figure 2 The pooled overall nationwide prevalence of HS in CHB patients. HS, hepatic steatosis; CHB, chronic hepatitis B.

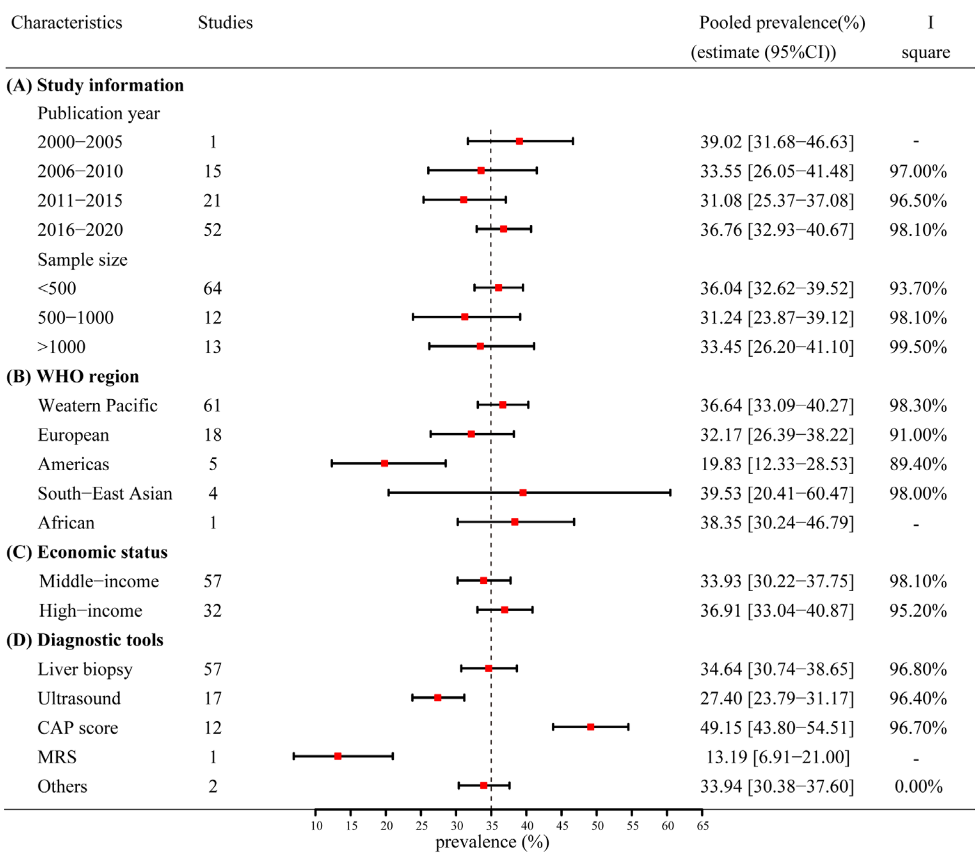

Figure 3 The forest plots of the meta-analysis on demographic and diagnostic features. CI, confidence interval; WHO, World Health Organization; CAP, controlled attenuation parameter; MRS, magnetic resonance spectroscopy.

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

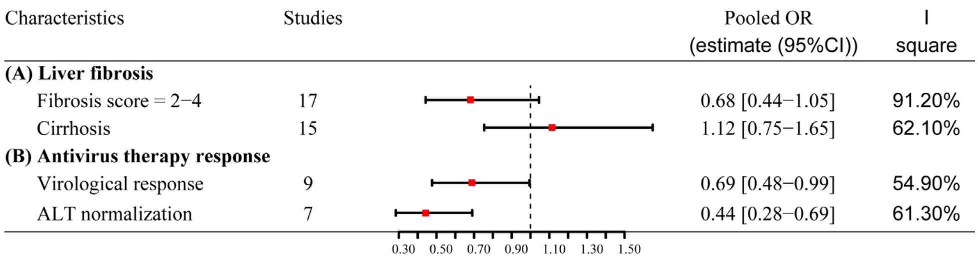

Figure 4 The forest plots of the meta-analysis on the impact of HS on fibrosis progression and the effectiveness of antiviral therapy in CHB patients. CI, confidence interval; ALT, alanine transaminase; OR, odds ratio.

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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Supplementary

Search strategy

The search terms comprising combinations of different Medical Subject Headings (MeSH) terms were applied for the three English databases (PubMed, EMBASE and Cochrane Library). The details are shown as follows:
Pubmed
#1: (Hepatitis B[MeSH]) OR (Hepatitis B, Chronic [MeSH]) OR (Hepatitis B virus [MeSH]) OR (Hepatitis B Antigens [MeSH]);
#2: (Hepatitis B[Title/Abstract]) OR (HBV[Title/Abstract]) OR (B virus, Hepatitis[Title/Abstract]) OR (Dane Particle[Title/Abstract]) OR (Particle, Dane[Title/Abstract]) OR (type b hepatitis [Title/Abstract]) OR (HBAg[Title/Abstract]) OR (B Antigens, Hepatitis[Title/Abstract]);
#3: #1 OR #2;
#4: (Fatty Liver [MeSH]) OR (Non-alcoholic Fatty Liver Disease [MeSH]);
#5: (steatohepat*[Title/Abstract]) OR (Steatosis [Title/Abstract]) OR (Steatoses [Title/Abstract]);
#6:(Non alcoholic Fatty Liver Disease [Title/Abstract]) OR (NAFL*[Title/Abstract]) OR (NASH[Title/Abstract]) OR (Liver [Title/Abstract] AND (fatty [Title/Abstract] OR steato*[Title/Abstract]));
#7: #4 OR #5 OR #6;
#8: #3 AND #7.
Result: 2168
Embase
#1: 'hepatitis b'/exp;
#2: 'chronic hepatitis b'/exp;
#3: 'hepatitis b virus'/exp;
#4: 'hepatitis b antigen'/exp;
#5: #1 OR #2 OR #3 OR #4;
#6: 'hbv': ab,ti;
#7: 'hepatitis b': ab,ti;
#8: 'b virus, hepatitis': ab,ti;
#9: 'dane particle': ab,ti;
#10: 'type b hepatitis': ab,ti;
#11: 'hbag': ab,ti;
#12: 'b antigens, hepatitis': ab,ti;
#13: #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12;
#14: #5 OR #13;
#15: 'fatty liver'/exp;
#16: 'nonalcoholic fatty liver'/exp;
#17: steatohepat*: ab,ti;
#18: 'steatosis': ab,ti;
#19: 'steatoses': ab,ti;
#20: 'non alcoholic fatty liver disease': ab,ti;
#21: 'nafl*': ab,ti;
#22: 'nash': ab,ti;
#23: 'fatty': ab,ti;
#24: 'steato*': ab,ti;
#25: #23 OR #24;
#26: 'liver': ab,ti;
#27: #25 AND #26;
#28: #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #27;
#29: #14 AND #28.
Result: 7118
Cochrance
#1: MeSH descriptor: [Hepatitis B] explode all trees
#2: MeSH descriptor: [Hepatitis B Antigens] explode all trees
#3: MeSH descriptor: [Hepatitis B virus] explode all trees
#4: #1 or #2 or #3
#5: (HBV): ti,ab,kw
#6: (hepatitis b): ti,ab,kw
#7: (B virus, Hepatitis): ti,ab,kw
#8: (Dane Particle): ti,ab,kw
#9: (type b hepatitis): ti,ab,kw
#10: (HBAg):ti,ab,kw
#11: (B Antigens, Hepatitis): ti,ab,kw
#12: #5 or #6 or #7 or #8 or #9 or #10 or #11
#13: #4 or #12
#14: MeSH descriptor: [Fatty Liver] explode all trees
#15: MeSH descriptor: [Non-alcoholic Fatty Liver Disease] explode all trees
#16: (steatohepat*): ti,ab,kw
#17: (steatosis): ti,ab,kw
#18: (steatoses): ti,ab,kw
#19: (non alcoholic fatty liver disease): ti,ab,kw
#20: (nafl*): ti,ab,kw
#21: (nash): ti,ab,kw
#22: (fatty): ti,ab,kw
#23: (steato*): ti,ab,kw
#24: #22 OR #23
#25: (liver): ti,ab,kw
#26: #24 AND #25
#27: #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #26
#28: #27 AND #13
Resuslt: 225

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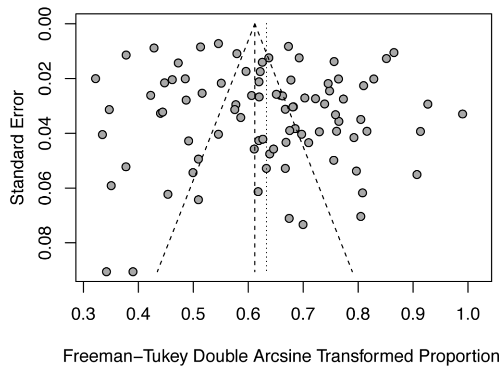

Figure S1 Funnel plots of the HS prevalence in CHB patients were used to assess publication bias. HS, hepatic steatosis; CHB, chronic hepatitis B.

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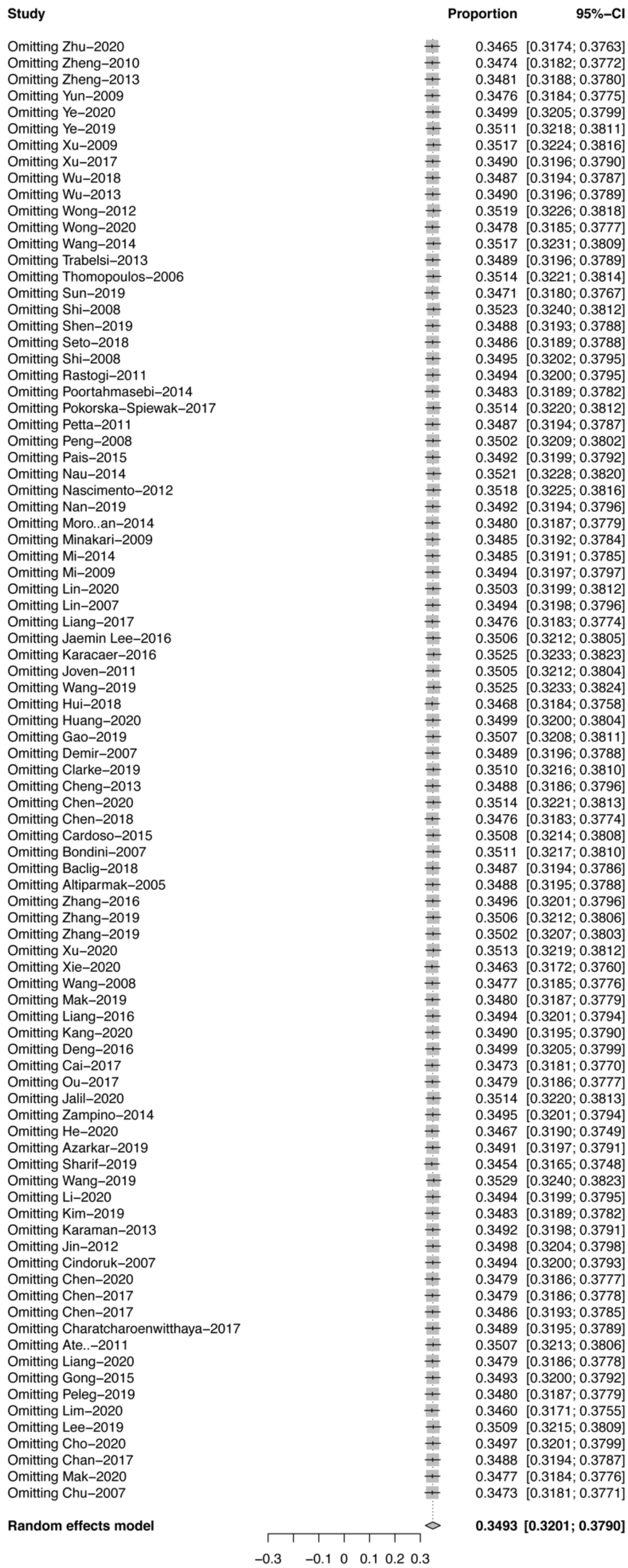

Figure S2 Sensitivity analysis of omitting each study on the overall pooled estimate of the prevalence of HS in CHB patients. HS, hepatic steatosis; CHB, chronic hepatitis B.

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Table S1 Diagnostic criteria of HS in CHB patients

Defined as HS	Studies	Pool prevalence (%), estimate (95%CI)	I^2	P value between groups
Liver biopsy (affected hepatocytes)				<0.0001
>5%	40	35.81 (31.13–40.63)	97.30%	
>10%	3	20.35 (17.64–23.20)	0.00%	
Others	9	32.56 (21.50–44.66)	95.60%	
CAP score				0.0549
≥248 dB/m	5	43.50 (38.33–48.73)	91.30%	
≥238 dB/m	3	57.27 (45.49–68.64)	95.10%	
Others	4	50.44 (44.41–56.46)	91.20%	

Interpretation of the diagnostic criteria of HS in CHB patients: (I) Liver biopsy: liver biopsy is the gold standard diagnostic method as well as the most commonly used method for HS diagnosis in the studies (57/90). The prevalence of HS in CHB was also stratified by diagnostic criteria for HS using liver biopsy. HS defined as 10% or more of hepatocytes affected had a lower prevalence rate of HS in CHB patients (20.35%; 95% CI: 17.64–23.20%) than that of HS defined as 5% or more (35.81%; 95% CI: 31.13–40.63%). Furthermore, HS defined as 5% or more of hepatocytes affected was the dominant diagnostic criteria (40/52) for HS using liver biopsy. (II) CAP score: the lower limit of the CAP score to determine HS in CHB patients was slightly heterogeneous (220–248 dB/m). The subgroup analysis showed that HS defined as CAP ≥248 dB/m (43.50%; 95% CI: 38.33–48.73%) had a lower prevalence rate of HS in CHB patients than that of HS defined as CAP ≥238 dB/m (57.27%; 95% CI: 45.49–68.64%). However, due to the limited subgroup studies reporting CAP scores, we cannot draw a straightforward conclusion to determine the heterogeneity associated with the diagnostic CAP score. (III) Abdominal ultrasonography: HS was assessed using criteria including the presence of liver and kidney echo discrepancy, with or without the presence of posterior attenuation of ultrasound beam, vessel blurring, difficult visualization of the gallbladder wall, and difficult visualization of the diaphragm. CAP, controlled attenuation parameter; HS, hepatic steatosis; CHB, chronic hepatitis B.

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Table S2 The studies and characteristics included in this meta-analysis

No	Author, year	Country	Study period	Study design	Diagnostic tools	Sample size	Hepatic steatosis in CHB patients
1	Zhu, 2020 (36)	China	2017.1–2019.12	Cross-sectional study	Liver biopsy	82	51
2	Zheng, 2010 (37)	China	2005.5–2009.3	Cross-sectional study	Liver biopsy	204	106
3	Zheng, 2013 (13)	China	2008.1–2011.6	Cross-sectional study	Liver biopsy	291	132
4	Yun, 2009 (38)	Korea	2005.1–2006.3	Cross-sectional study	Liver biopsy	86	44
5	Zheng, 2010 (39)	China	2001.1–2009.1	Case-controlled study	Liver biopsy	36	18
6	Ye, 2020 (40)	China	2015.2–2018.12	Prospective cohort study	Liver biopsy	440	85
7	Ye, 2019 (41)	China	2011.1–2018.12	Cross-sectional study	Ultrasound	1,223	253
8	Xu, 2017 (35)	China	2012.7–2014.4	Cross-sectional study	Liver biopsy	366	137
9	Wu, 2018 (42)	China	2019.12–2018.3	Cross-sectional study	Liver biopsy	272	108
10	Wu, 2013 (43)	China	2016–2010	Cross-sectional study	Liver biopsy	89	34
11	Wong, 2012 (44)	China	NA	Cross-sectional study	MRS	91	12
12	Wong, 2020 (45)	Malaya	2013–2017	Cohort study	Fibroscan	614	294
13	Wang, 2014 (46)	China	2002–2011	Cross-sectional study	Liver biopsy	3,212	554
14	Trabelsi, 2013 (47)	Tunisie	2002–2011	Cross-sectional study	Liver biopsy	133	51
15	Thomopoulos, 2006 (48)	Greece	1999.1–2004.12	Cross-sectional study	Liver biopsy	233	42
16	Sun, 2019 (49)	China	2014.3–2017.3	Cross-sectional study	Fibroscan	615	334
17	Shi, 2008 (50)	China	2005.1–2007.6	Cross-sectional study	Liver biopsy	1,915	260
18	Shen, 2019 (51)	China	2014.2–2015.8	Cross-sectional study	Liver biopsy	593	233
19	Seto, 2018 (52)	China	2015.1–2016.9	Cross-sectional study	Fibroscan	1,606	655
20	Shi, 2008 (53)	China	2005.1–2008.4	Cohort study	Liver biopsy	119	39
21	Rastogi, 2011 (54)	India	NA	Cross-sectional study	Liver biopsy	350	118
22	Poortahmasebi, 2014 (55)	Iran	2010–2011	Cross-sectional study	Liver biopsy	160	71
23	Petta, 2011 (56)	Italy	2000.1–2008.12	Cohort study	Liver biopsy	170	68
24	Peng, 2008 (24)	China	2002–2006	Cross-sectional study	Liver biopsy	153	41
25	Pan, 2015 (57)	China	2012.1–2013.6	Case-controlled study	Liver biopsy	108	57
26	Pais, 2015 (58)	Romania	2010.7–2013.4	Cross-sectional study	Others	110	39
27	Nascimento, 2012 (59)	Brazil	2010.1–2011.10	Retrospective transversal study	Liver biopsy	30	3
28	Nan, 2019 (60)	China	2017.1–2018.12	Cross-sectional study	Fibroscan	1,621	574
29	Minakari, 2009 (61)	Iran	NA	Cross-sectional study	Liver biopsy	132	56
30	Mi, 2014 (62)	China	2012.7–2013.12	Cross-sectional study	Liver biopsy	340	142
31	Mi, 2009 (63)	China	2005.1–2008.6	Cross-sectional study	Liver biopsy	1,263	422
32	Lin, 2020 (64)	China	2016.4–2018.4	Cross-sectional study	Ultrasound	4,734	1275
33	Lin, 2007 (65)	China	2004.1–2005.12	Cross-sectional study	Ultrasound	817	277
34	Liang, 2017 (66)	China	2013.9–2015.6	Cross-sectional study	Liver biopsy	65	34
35	Joven, 2011 (67)	Spain	NA	Cross-sectional study	Liver biopsy	60	14
36	Hui, 2018 (9)	China	2014.12–2016.7	Case-controlled study	Fibroscan	1,548	876
37	Huang, 2020 (68)	China	2016.4–2018.2	Cross-sectional study	Ultrasound	2,110	632
38	Gao, 2019 (69)	China	2014.5–2017.12	Cross-sectional study	Ultrasound	3,477	838
39	Demir, 2007 (70)	Turkey	NA	Cross-sectional study	Liver biopsy	49	19
40	Clarke, 2019 (71)	USA	2004–2015	Cohort study	Ultrasound	617	134
41	Chen, 2020 (72)	China	2013.10–2018.8	Cross-sectional study	Liver biopsy	535	100
42	Cardoso, 2015 (73)	France	2002.11–2004.12	Cohort study	Liver biopsy	136	30
43	Bondini, 2007 (74)	USA	2000.10–2006.6	Cross-sectional study	Liver biopsy	64	12
44	Baclig, 2018 (75)	Philippines	2012.1–2013.12	Cross-sectional study	Liver biopsy	46	19
45	Altiparmak, 2005 (76)	Turkey	1997–2002	Cross-sectional study	Liver biopsy	164	64
46	Zhang, 2016 (77)	China	2011.1–2015.1	Cross-sectional study	Liver biopsy	364	118
47	Zhang, 2019 (78)	China	2013.7–2018.2	Cross-sectional study	Liver biopsy	387	94
48	Zhang, 2019 (79)	China	2013.7–2018.2	Cross-sectional study	Liver biopsy	530	145
49	Yang, 2017 (80)	China	2012.5–2014.5	Case-controlled study	Liver biopsy	39	22
50	Xu, 2020 (81)	China	2014.1–2017.12	Cohort study	Liver biopsy	601	119
51	Xie, 2020 (82)	China	2017.3–2018.3	Cross-sectional study	Liver biopsy	161	101
52	Wang, 2008 (83)	China	NA	Cross-sectional study	Ultrasound	50	26
53	Mak, 2019 (84)	China	2015.1–2016.9	Cohort study	Fibroscan	415	192
54	Pan, 2017 (85)	China	2012.1–2013.6	Case-controlled study	Liver biopsy	99	52
55	Liang, 2016 (86)	China	2013.9–2015.4	Case-controlled study	Liver biopsy, US	137	46
56	Kang, 2020 (87)	China	2009.1–2014.6	Cross-sectional study	Liver biopsy	360	146
57	Deng, 2016 (88)	China	2013.3–2015.3	Cross-sectional study	Liver biopsy	254	75
58	Cai, 2017 (89)	China	2013.1–2915.12	Cross-sectional study	Liver biopsy	488	256
59	Ou, 2017 (90)	China	2013.6–2016.1	Cross-sectional study	Fibroscan	1,312	618
60	Liu, 2019 (91)	China	2016.1–2018.8	Case-controlled study	Liver biopsy	248	124
61	Jalil, 2020 (92)	PAK	2016.7–2017.5	Cross-sectional study	Ultrasound	240	44
62	Zampino, 2014 (93)	Italy	2009–2013	Case-controlled study	Liver biopsy	66	22
63	Azarkar, 2019 (94)	Iran	2013–2014	Case-controlled study	Ultrasound	376	138
64	Sharif, 2019 (95)	PAK	2018.6–2019.5	Cross-sectional study	Fibroscan	230	161
65	Xu, 2009 (96)	China	2007.1–2008.3	Cross-sectional study	Ultrasound	365	61
66	Pokorska, Spiewak, 2017 (97)	Poland	2002–2013	Cross-sectional study	Liver biopsy	30	4
67	Nau, 2014 (98)	Brazil	2011.8–2012.9	Cross-sectional study	Ultrasound	71	8
68	Moroşan, 2014 (99)	Romania	NA	Cross-sectional study	Liver biopsy	100	47
69	Lee, 2016 (100)	Korea	2009.1–2012.12	Retrospectively cohort study	Ultrasound	102	24
70	Karacaer, 2016 (101)	Turkey	2012.1–2014.10	Cross-sectional study	Liver biopsy	254	29
71	Wang, 2019 (102)	China	2011.10–2014.3	Cohort study	Ultrasound	152	16
72	Cheng, 2013 (103)	China	2002–2009	Cross-sectional study	Ultrasound	3,642	1416
73	Chen, 2018 (104)	China	2015.1–2017.4	Cross-sectional study	Liver biopsy	144	73
74	Zhao, 2011 (105)	China	2008.4–2009.12	Case-controlled study	Liver biopsy	70	30
75	He, 2020 (106)	China	2014.12–2018.8	Cross-sectional study	Fibroscan	2,266	1313
76	Zhu, 2016 (107)	China	2008.6–2013.6	Case-controlled study	Ultrasound	125	61
77	Xu, 2015 (108)	China	2005–2009	Case-controlled study	Liver biopsy	50	22
78	Wang, 2019 (109)	China	2010.1–2018.3	Cohort studies	Liver biopsy	622	62
79	Li, 2020 (110)	USA	2000–2016	Cohort studies	Others	555	187
80	Kim, 2019 (111)	Korea	2007–2016	Cohort studies	Fibroscan	334	146
81	Karaman, 2013 (14)	Turkey	2005–2010	Cohort studies	Liver biopsy	119	43
82	Jin, 2012 (32)	China	2007.1–2009.11	Cohort studies	Ultrasound	213	65
83	Cindoruk, 2007 (112)	Turkey	2002.10–2006.1	Cross-sectional study	Liver biopsy	140	48
84	Chen, 2020 (15)	China	2003.4–2016.10	Cohort studies	Liver biopsy	196	94
85	Chen, 2017 (113)	China	2008.3–2010.3	Cohort study	Liver biopsy	162	77
86	Chen, 2017 (114)	China	2013.3–2014.3	Cohort study	Fibroscan	153	63
87	Charatcharoenwitthaya, 2017 (115)	Thailand	2010–2013	Cohort study	Liver biopsy	256	98
88	Ateş, 2011 (116)	Turkey	2006.12–2009.7	Cross-sectional study	Liver biopsy	84	19
89	Liu, 2016 (117)	China	2012.1–2014.12	Case-controlled study	CT	60	40
90	Liang, 2020 (118)	China	2010.3–2016	Cohort study	Liver biopsy	226	107
91	Gong, 2015 (119)	China	2010.1–2013.12	Cohort study	Liver biopsy	89	31
92	Peleg, 2019 (10)	Israel	2007.1–2017.12	Cohort study	Liver biopsy	524	241
93	Lim, 2020 (120)	Singapore	2000.1–2014.12	Cohort study	Liver biopsy	289	185
94	Lee, 2019 (29)	Korea	2007.1–2015.12	Retrospective cohort study	Liver biopsy	321	70
95	Cho, 2020 (28)	Korea	2009.1–2015.12	Cohort study	Ultrasound	826	260
96	Chan, 2017 (12)	China	2006.1–2009.12	Cohort study	Liver biopsy	270	107
97	Mak, 2020 (121)	China	2015.1–2016.9	Cohort study	Fibroscan	330	161
98	Chu, 2007 (27)	China	2001–2004	Cross-sectional study	Ultrasound	162	86

Table S3 Relationship between HBV viral load and HS in CHB patients

Characteristics	Studies	Pooled OR or WMD, estimate (95% CI)	I^2	P value
DNA >1,000 copies/mL	3	0.57* (0.31–1.03)	77.70%	0.0636
DNA >5,000 copies/mL	3	0.88* (0.61–1.27)	40.70%	0.1851
DNA (lg IU/mL)	14	−0.35 (−0.89–0.19)	97.60%	0.2096

*OR, odds ratio; WMD, weighted mean difference; HBV, hepatitis B virus; HS, hepatic steatosis; CHB, chronic hepatitis B.

Table S4 The influence of the diagnostic mode of HS on the outcomes

Defined as hepatic steatosis	Studies	Pooled OR, estimate (95% CI)	I^2	P value
Cirrhosis				>0.05
Liver biopsy (affected hepatocytes) >5%	10	1.17 (0.74–1.86)	72.80%	
Liver biopsy (affected hepatocytes) >0%	1	5.00 (0.23–107.28)	–	
CAP >238 dB/m	1	1.35 (0.14–13.13)	–	
Unclear	3	0.77 (0.37–1.59)	0.00%	
Fibrosis score 2–4				>0.05
Liver biopsy (affected hepatocytes) >5%	11	0.75 (0.49–1.14)	87.80%	
Liver biopsy (affected hepatocytes) >0%	2	1.04 (0.61–1.77)	0.00%	
CAP >238 dB/m	1	0.78 (0.51–1.19)	–	
Unclear	3	0.35 (0.03–4.29)	97.50%	

OR, odds ratio; CAP, controlled attenuation parameter.

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