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Prevalence of hepatic steatosis, fibrosis and associated factors in chronic hepatitis B

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Summary

Background: As the prevalence of hepatitis steatosis (HS) increases, the prevalence of HS among those with chronic hepatitis B (CHB) may also be increasing but data on the effect of HS on CHB disease progression are lacking.

Aims: To determine the prevalence of HS in CHB and associated factors, prevalence of fibrosis and its association with HS.

Methods: Two researchers independently searched the literature and extracted data. We included full-length original articles of adults with CHB that evaluated. Prevalence estimates were pooled using a random-effects model. Associations between HS and fibrosis were assessed by pooled odds ratios (ORs) or mean differences (MD).

Results: Of the 2821 records screened, 54 eligible studies (28 648 patients) were analysed. The pooled prevalence of HS in CHB was 32.8% (95% CI, 28.9-37.0) with higher prevalence in men and obese patients. Older age, male sex and metabolic factors were associated with HS while an inverse association was observed between HS and HBeAg (OR 0.82, 95% CI, 0.75-0.91) and HBV DNA levels (MD −0.38, 95% CI −1.16-−0.42). The pooled prevalence of significant fibrosis (≥F2 or ≥F3) was similar between patients with CHB with or without HS (40.1% vs 42.22%, $P = 0.68$). HS was not significantly associated with fibrosis (pooled OR 0.87, 95% CI 0.54-1.39, 20 studies, 6232 patients).

Conclusions: Approximately 30% of patients with CHB had HS, which was positively associated with male sex, diabetes and metabolic factors, and was negatively associated with HBeAg and HBV DNA. HS was not significantly associated with increased fibrosis.

Qi Zheng and Biyao Zou are contributed equally. The Handling Editor for this article was Professor Grace Wong, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Chronic hepatitis B (CHB) is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide and the leading cause of liver-related morbidity and mortality.[1,2] As non-alcoholic fatty liver disease (NAFLD) is also prevalent globally including Asia where CHB is endemic,[3,4] the co-existence of hepatic steatosis (HS) with CHB is likely to be common.

Prior studies have shown that both host and viral factors may contribute to the development of HS in chronic hepatitis C (CHC) patients, leading to more rapid fibrosis progression and poorer response to interferon-based anti-viral therapy.[5] However, the prevalence of HS in CHB patients and the relationship between HS and CHB as well as the prevalence of significant fibrosis with HS and the association between HS and fibrosis in CHB patients have not been well-characterised. Reported data have generally been limited to studies of small sample sizes, based only on histology or imaging, single-centre or single-country/region experience and/or limited to HS prevalence and not factors associated with HS or fibrosis in patients with HS.[3-12]

Therefore, the aims of this study were to determine the prevalence and factors associated with HS in CHB, the prevalence of fibrosis in HS and whether HS was associated with increased fibrosis in CHB patients.

2 | METHODS

2.1 | Search terms

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines which is listed in the supplemental file. Electronic searches were performed in PubMed, Embase and the Cochrane library from the inception of the database to May 28, 2019, without language restriction, using various combinations of the keywords and to include medical subject headings terms, which can be found in detail in the Supplemental Method. The search strategy was developed in collaboration with an experienced medical librarian. Briefly, for Pubmed, we used the term NAFLD or hepatic steatosis and related terms in combination with CHB and its related terms to search for relevant articles. Similar strategies were used for the other databases. In addition, we manually searched the references of the included articles and relevant systematic reviews for additional articles.

All literature search, article screening, data extraction and quality assessment were performed independently by two researchers. Discrepancies were resolved by discussion and consensus; and if necessary, a third reviewer was involved.

2.2 | Eligibility criteria

The details of the study inclusion and exclusion criteria are listed in the supplemental file. Briefly, we included full-length original research articles of adult CHB patients that included assessment for HS, excluded other concurrent liver disease such as viral hepatitis C (HCV) or human immunodeficiency virus (HIV) co-infected, autoimmune hepatitis, Wilson's disease, and reported at least one of the study outcomes. We excluded studies on special populations such as pregnant persons, duplicate studies from same cohort and studies with small sample size of less than 50.

2.3 | Data extraction

The following data were collected from each study using a case report form developed specifically for this study: last name of the first author, gender, mean or range of age, design of the study, ethnicity, country of origin, year of publication, year of study, sample size, risk factors and the number of patients affected and not affected. For duplicate published data or studies with overlapping data, only the newest or the most comprehensive publication was extracted and included in the analysis. For studies that reported the risk estimates in different models, the results of the most adjusted model were collected.

2.4 | Risk-of-bias assessment

We used a risk-of-bias tool modified from the Newcastle-Ottawa quality assessment scale (NOS) to assess the quality of individual reports.[13] The NOS is a scoring tool comprising 7 items with 9 scores that assesses how well the investigators selected their participants (score ranges from 0 to 4), how comparable their results may be (score ranges from 0 to 2), and how applicable the outcomes are (score ranges from 0 to 3). In this review of prevalence data, to better capture the quality of the included studies, we gave more weight for the selection score to range up to 5 because we assigned up to 2 points for the ascertainment of the diagnostic tool of NAFLD, since the prevalence can be greatly affected by the diagnostic methods. We also assigned up to 1 point for the sample size element of the selection score since data of small studies can be subject to bias. As a result, we decrease outcomes score to 1 from 3 to yield a total of 9 points as originally proposed by the NOS system. The higher the score, the better the quality of the study and the lower the risk of bias. We categorised the studies as good quality if the total score was 7 or more, fair if the score was 4-6 and poor if the score was <4.

2.5 | Outcomes

The main outcomes were overall pooled prevalence of HS in CHB patients and pooled significant (≥ F2) or advanced (F3-F4) fibrosis prevalence among CHB patients with and without HS. The secondary outcomes were the factors associated with HS in CHB patients as well as the association between fibrosis and HS in patients with CHB.

2.6 | Statistical analysis

According to the expected heterogeneity across studies, a random-effects model with logit transformation was used to calculate the pooled prevalence and 95% confidence intervals (CIs). Odds ratios (OR) were used to describe the association between binary variables and outcomes while mean difference (MD) was used with continuous variables where MD measures the absolute difference between the mean value in group with HS and the group without HS. We estimated the pooled MD using the random-effect model. We used standard normal distribution to obtain the confidence interval of individual studies and Q-Profile method[14] to obtain the confidence interval for the between-study variance. In this study, we used MD for the following continuous variables: age, body mass index (BMI), waist circumference, total cholesterol, triglyceride, glucose, hepatitis B virus (HBV) DNA, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). We used generalised linear mixed model (GLMM) - more specifically, a random intercept logistic regression model - for the meta-analysis of proportions.[15]

We estimated heterogeneity between studies using Higgins' and Thompson's I^2 statistics derived from Cochran's Q test ($I^2 \geq 50\%$ or higher indicated at least moderate heterogeneity). Subgroup analyses were performed using study level data to determine the factors contributing to observed heterogeneity which included individual associations between the pooled estimates and the following covariates: gender, presence of obesity, region, HBeAg status, mean HBV DNA level (cut-off at 5 log IU/mL), median of study year (cut-off at 2007). The cut-offs of HBV DNA and study year categories were based on mean or median values of included studies. Funnel plots and Egger's test were used to assess for publication bias. $P < 0.05$ was considered statistically significant, and all statistical analyses were performed using the '*meta*' packages in R statistical software (version 3.5.2). The study was conducted in accordance with the ethics principles of the Declaration of Helsinki in 1975, as revised in 2008 and was not a human subject study as it only involved aggregated published data.

3 | RESULT

3.1 | Study selection

We identified 2821 records and excluded 2686 ineligible records based on reviewing the title and abstracts, leaving 135 potentially eligible studies which were retrieved for full-text reviews. A total of 54 articles (28 648 CHB patients) met our inclusion criteria and were included in the meta-analysis (Figure 1, Supplemental Reference). We analysed 53 studies (n = 28 233) for factors associated with HS, and for the overall and subgroup prevalence of HS in CHB, and 20 studies (n = 6232) for fibrosis prevalence as well as association between HS and fibrosis. One of the 20 articles included in the analysis of fibrosis was excluded from the analysis of HS prevalence due to overlapping cohort. All articles were published in English except two in Chinese language.

3.2 | Study patient characteristics

The majority of the studies were from Asian countries/regions (Mainland China [n = 22], Hong Kong [n = 3], South Korea [n = 5], Taiwan [n = 4], Thailand [n = 1] and India [n = 1]). Other countries represented in this study were from the Middle East or West Asia (Iran, Turkey) [n = 8], Europe (France, Spain, Romania, Italy, Greece) [n = 6], North America (USA) [n = 2] and South America (Brazil) [n = 1]. In total, 16 countries/regions and four continents were represented. The sample sizes ranged from 64 to 3926 individuals, and the study periods ranged from 1997 to 2016. The overall mean age in individual studies ranged from 22 to 58.2 years. Of the 54 studies, 38 used liver biopsy and five used transient elastography (TE) with controlled attenuation parameter (CAP) to assess fibrosis stage and HS, and 11 used ultrasound for the diagnosis of HS. Twenty of the 54 studies were analysed for fibrosis prevalence in CHB with HS. The characteristics of the 53 included studies for HS prevalence are presented in Table S1.

3.3 | The prevalence of HS among patients with CHB

The overall pooled HS prevalence among patients with CHB from 53 studies was 32.83% (95% CI 28.92-37.00; $I^2 = 98.0\%$). (Table 1) Due to the characteristics of different study populations, we stratified HS prevalence among CHB patients by gender, body mass index (BMI), geographic region, HBeAg status, HBV DNA levels, median of study year and HS diagnostic method. There were no statistically significant differences in HS pooled depending on geographic regions (Middle East > Asia > Europe) ($P = 0.31$) and HS diagnostic method ($P = 0.92$). (Table 1) However, the pooled prevalence of HS among CHB patients was significantly higher in males 34.70% compared to females 24.94% ($P = 0.009$).

Regarding body mass index (BMI), nine studies provided data for the obese populations (987 participants) and non-obese (normal and overweight) populations (5457 participants) for our subgroup analysis by weight status. The definitions used for overweight and obese populations in each study varied. Many studies used the WHO cut-offs for Asians in which a BMI = 23.0-27.5 kg/m² was defined as overweight and ≥27.5 kg/m² as obese rather than the BMI cut-offs for western countries. Therefore, we grouped patients according to the definitions used by the studies into obese and non-obese (normal or overweight BMI) population. The pooled data for HS prevalence among CHB patients in the obese population was 51.76% (n = 9 studies and 987 patients) which was 2.5 times higher than the prevalence in the non-obese population (20.49%; n = 9 studies and 5457 patients). (Table 1) Heterogeneities were substantial across the vast majority of study domains.

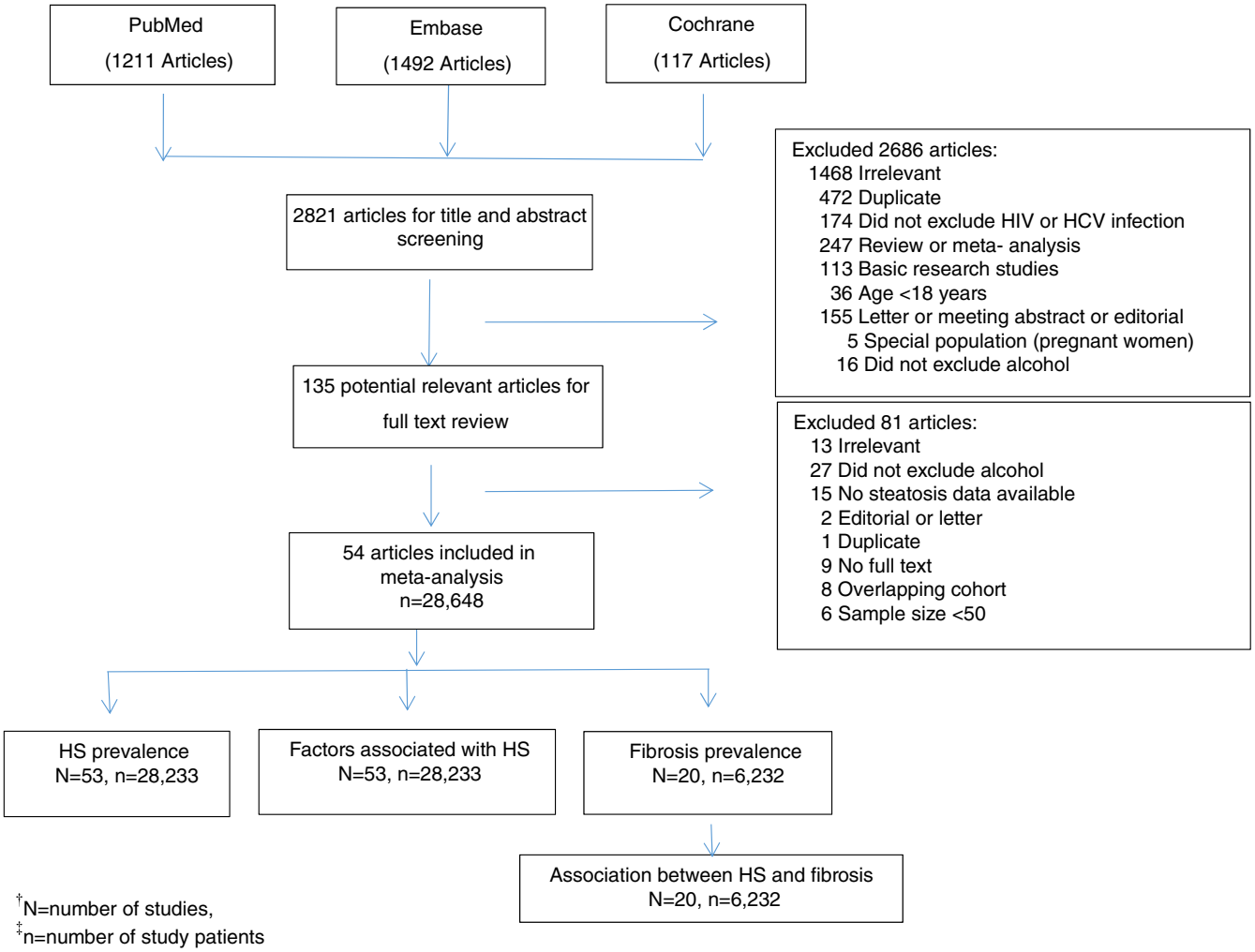

FIGURE 1 Systematic literature search and screening for epidemiology in chronic hepatitis B (CHB) with hepatic steatosis (HS)

3.4 | Factors associated with HS in CHB patients

A pooled meta-analysis of ORs and MDs relating various factors to the presence of HS in CHB patients are shown in Table 2. Male gender (OR, 1.49; 95% CI, 1.25-1.76, $P < 0.0001$), diabetes (OR, 2.20; 95% CI 1.47-3.29, $P = 0.0001$) or metabolic syndrome (OR, 3.81; 95% CI 2.28-6.35, $P < 0.0001$) were significantly associated with HS. Similarly, BMI (MD, 3.85; 95% CI 2.68-5.03), waist circumference (MD, 9.22; 95% CI 5.55-12.91), total cholesterol (MD, 26.11; 95% CI 14.21-38.00) and triglycerides (MD, 38.42; 95% CI 14.07-62.76) were associated with HS (all $P < 0.001$). Older age also had a positive association with HS (MD, 2.17; 95% CI, 0.95-3.39, $P = 0.0005$).

CHB patients were less likely to have HS, if they were HBeAg+ (OR, 0.82; 95% CI 0.75-0.91, $P < 0.0001$) while HBV DNA levels (MD, −0.38; 95% CI −1.16-−0.42, $P = 0.35$) were inversely associated with HS. The grade of necroinflammatory activity of hepatic histology index (HAI) was not significantly associated with the presence of HS. However, serum enzyme AST was negatively correlated with HS (MD, −10.84; 95% CI −20.94-−0.74, $P = 0.04$) (Table 2) Heterogeneity ranged from a low of 0.30% for HBeAg to a high 98.7% for triglycerides.

3.5 | Prevalence of significant or advanced fibrosis in CHB patients with and without HS

Twenty studies (6232 patients) provided data for the analysis of fibrosis prevalence (Table 3). Of the 20 studies, 17[16,17,19-23,25-34] evaluated fibrosis by liver histology and 3[18,24,35] were assessed by transient elastography. Among the 17 studies using histology, fibrosis stage of 15 studies was from F0-F4 according to Knodell or METAVIR system, and only two studies using the F0-F6 via the Ishak system. Data of significant fibrosis (≥F2) or advanced fibrosis (≥F3) were obtained as reported by the different scoring systems. The overall pooled proportions of significant or advanced fibrosis prevalence in those with CHB and HS was 40.09% (95% CI, 33.64-46.90) which was similar to that of CHB without HS (42.25%; 95% CI, 34.89-49.97) ($P = 0.68$). (Table 4) Additionally, in separate sub-analysis by degree of fibrosis, there was no

TABLE 1 Pooled prevalence of hepatic steatosis (HS) in chronic hepatitis B (CHB) patients

Study population	Studies (N)	Participants (n)	HS (n)	HS prevalence (%)
Total overall population	53	28 233	8157	32.83
Gender				
Male	31	9703	2810	34.70
Female	30	5227	1024	24.94
BMI[a]				
Obese	9	987	460	51.76
Non-obese	9	5457	784	20.49
Region[b]				
Middle East	8	1032	405	38.11
Asia	36	26 721	7679	33.39
Europe	6	764	227	29.62
HBeAg				
Positive	21	6409	1229	27.35
Negative	23	6938	1541	30.99
HBVDNA				
<5 log IU/mL	10	4978	870	24.38
≥5 log IU/mL	10	1379	455	33.16
Median of study year				
1999-2007	22	11 179	2923	30.98
2008-2016	25	13 355	4725	35.92
Diagnostic method				
Liver biopsy	38	12 880	3391	33.23
Ultrasound	11	10 865	3198	31.27
Controlled attenuation parameter	4	4488	1568	33.58

Note: HBV DNA and study year categories were based on mean or median values of included studies. I^2 for all analyses >72%.

[a]Obese population: Defined as body mass index (BMI) ≥25-28kg/m^2; non-obese population: Defined as body mass index (BMI) <25-28kg/m^2

[b]No results presented for Africa and the Americas due to lack of data.

significant difference between the proportion of significant fibrosis (≥F2) prevalence ($P = 0.28$) (13 studies and 4946 patients) and of advanced fibrosis (≥F3) prevalence ($P = 0.06$) (7 studies and 1286 patients). (Table 4) There was also no significant difference in the prevalence of significant or advanced fibrosis in CHB patient with HS in stratified analysis by HS diagnostic method ($P = 0.62$). (Table 4) Heterogeneity ranged from a low I^2 of 0.0% to a high of 95.6%.

3.6 | Association between HS and fibrosis in CHB patients

Twenty studies (6232 patients) provided data for our pooled analysis for the association between HS and fibrosis in CHB. HS was not significantly associated with the presence of significant (≥F2) or advanced fibrosis (≥F3) (OR 0.87, 95% CI: 0.54-1.39) (Figure 2).

3.7 | Quality assessment and publication bias of included studies

The quality assessment scores for included studies are shown in the supplemental file (Tables S2 and S3). The mean quality assessment score was 8.55 (range 6-9) for analysis of HS and 7.6 (range 5-9) for analysis of fibrosis. Overall, 46 high-quality studies and 8 fair-quality studies were included in the meta-analysis. There was no significant publication bias for the 53 studies providing data for HS prevalence (Egger's test $P = 0.39$, Figure S1).

4 | DISCUSSION

In this systematic review and meta-analysis, we determined that the overall HS prevalence among patients with CHB was 32.83%. Our results are in line with the reported prevalence of NAFLD of about 30% from Asia and most other regions of the world, suggesting that

TABLE 2 Pooled estimated effect of factors associated with hepatic steatosis in patients with CHB from the random model with a unity link function [odds ratio (OR) or mean difference (MD)]

Factor	Studies (N)	Participants (n)	OR	MD	95% CI	*P*
Age	28	10 583		2.17	[0.95-3.39]	0.0005
Male gender	30	14 930	1.49		[1.25-1.76]	<0.0001
HAI ≥G2	10	3451	0.82		[0.46-1.46]	0.50
HAI =G2 or G3	14	3925	0.91		[0.57-1.45]	0.68
Diabetes	11	7766	2.20		[1.47-3.29]	0.0001
Metabolic syndrome	4	2379	3.81		[2.28-6.35]	<0.0001
Body mass index (kg/m^2)	20	6061		3.85	[2.68-5.03]	<0.0001
Waist circumference (cm)	6	3944		9.22	[5.55-12.91]	<0.0001
TC	21	6287		26.11	[14.21-38.00]	<0.0001
TG	18	5931	38.42		[14.07-62.76]	0.002
GLU	16	4431	10.04		[1.63-18.44]	0.019
HBeAg	22	13 151	0.82		[0.75-0.91]	<0.0001
HBV DNA	13	4717		−0.38	[−1.16-−0.42]	0.35
ALT	21	7042		−19.50	[−40.66-−1.66]	0.07
AST	19	6516		−10.84	[−20.94-−0.74]	0.04
GGT	14	5178		3.19	[−7.37-13.74]	0.55
ALP	12	2122		6.40	[−15.34-28.14]	0.56

the HS prevalence in CHB is similar to HS prevalence in the general population.[3,4] It is also in line with an earlier meta-analysis that found an HS prevalence of 29.6% among CHB patients though with much fewer patients,[36] although the prior meta-analysis only included 21 studies and 4100 HBV patients and did not exclude studies that included HCV patients. These results then suggest that approximately one in three adult patients with CHB may also have HS and care providers need to be cognizant that proper management of both conditions may be warranted, especially in high risk patients such as those with metabolic risk factors. Indeed, we found that CHB patients with metabolic syndrome had almost four times the odds of having HS compared to those without.

On the other hand, we found an inverse association between HS and HBeAg or HBV DNA level. The presence of HS was associated with an almost 20% less likelihood for having positive HBeAg and 0.38 unit decrease in HBV DNA level, suggesting that HS may have an inhibitory effect on viral replication. In fact, an inverse association between HS and HBV DNA levels has been reported previously, which suggested that HS may enhance viral clearance and inhibit HBV DNA replication.[37-39] Animal and transgenic mice model studies have also confirmed reduced HBV related antigen expression and viral replication in the presence of HS.[12,40,41] However, it is important that the above observed association was based on unadjusted analysis, so further controlled studies adjusting for background confounders are needed.

Contrary with the expectation of increased fibrosis by having both HS and CHB, we found similar proportions of significant fibrosis (≥F2 or ≥F3) among the HS and non-HS CHB populations (about 40% in both), without significant association between HS and fibrosis (pooled OR = 0.87, 95% CI 0.54-1.39). As also found in our study, the presence of HS was inversely associated with HBV DNA levels and there has been suggestion that reduced viral replication associated with HS may protect against fibrosis development. In fact, HS has also been reported to be associated with HBsAg seroclearance which also reduces the risk for fibrosis.[42,43] Nonetheless, further well-designed studies will be needed to elicit the mechanistic interactions between HBV and HS and lack of association between HS and fibrosis. Again, these observations were not all drawn from well-adjusted analyses, so additional large studies with appropriate adjustment for potential confounders are needed.

We also noted the high prevalence of significant fibrosis in CHB patients included in this analysis, regardless of HS presence. This is likely due to patient selection bias. The vast majority of fibrosis data in our study were derived from studies using liver biopsy to assess HS and fibrosis (17 of 20 studies, 1267 of 1631 patients), which may have selected for patients with more advanced disease, as liver biopsy is not recommended in most CHB patients. These studies are also more likely to be performed at tertiary care centres, which added another type of selection and referral bias towards more advanced patients. Regardless of the selection bias, we did not find a difference in fibrosis between those with and without HS in these study populations.

There are limitations of our current study. First, there was severe heterogeneity in the included studies although the quality of the individual studies was considered good or fair by NOS criteria. Furthermore, the methods used to ascertain exposure and outcomes varied across studies, which likely contributed to the heterogeneity. Specifically, different diagnostic methods and/or different ascertainment of HS by the

TABLE 3 Characteristics of studies included for analysis of fibrosis prevalence in chronic hepatitis B and hepatic steatosis (HS)

First Author	Publication Year	Region	Hepatic steatosis (n)	Overall Mean Age of HS patients, (yrs)	Overall Mean BMI of HS patients (kg/m^2)	Fibrosis (n)		Prevalence of fibrosis (%)	
						Hepatic steatosis	No hepatic steatosis	Hepatic steatosis	No hepatic steatosis
Altiparmak, E.[15]	2005	Middle East	64	37.9	27.75	11	20	17.18	20
Ates, F.[16]	2011	Middle East	19	50.5	32.9	8	27	42.11	41.54
Cai, S.[17]	2018	Asia	149	40.49	28.37	57	358	38.25	32.93
Charatcharoenwitthaya, P.[18]	2017	Asia	98	48.8	25.7	50	70	51.02	44.30
Chen, Y.[19]	2017	Asia	77	35.27	24.07	37	48	48.05	56.47
Dong, D. R.[20]	2015	Asia	30			19	29	63.33	65.91
Gong, L.[21]	2015	Asia	31	30.3	25.3	28	39	90.32	67.24
Kumar, M.[22]	2013	Asia	77			27	33	35.06	47.83
Mena, A.[23]	2014	Europe	23			11	13	47.83	17.81
Mi, Y. Q.[24]	2009	Asia	114		25.13	48	50	42.11	44.25
Peng, D.[25]	2008	Asia	41	36.56	25.29	9	21	21.95	18.75
Petta, S.[26]	2011	Europe	53			27	17	50.94	14.53
Poortahmasebi, V.[27]	2014	Middle East	71	39.13	26.67	32	25	45.07	28.09
Shi, J. P.[28]	2008	Asia	260	32	23	103	885	39.62	53.47
Thomopoulos, K. C.[29]	2006	Europe	42	46.2		17	77	40.48	40.31
Yun, J. W.[30]	2009	Asia	44			26	24	59.09	57.14
Zheng, R. D.[31]	2013	Asia	132	37.05	26.89	14	124	10.6	77.99
Zheng, R. D.[32]	2010	Asia	106	41.08	28.66	23	81	21.70	82.63
Nau, A. L.[33]	2014	South America	8	45.4	33.5	0	11	0	17.46
Mak, L. Y.[34]	2019	Asia	192		26.3	72	79	37.5	35.43

TABLE 4 Pooled prevalence and odds ratio of fibrosis in chronic hepatitis B patients with and without hepatic steatosis (HS)

Study group	Studies (N)	Participants (n)	Fibrosis (n)	Prevalence (%)	95% CI	*P*	Odds Ratio (95% CI)
Overall						0.68	0.87 (0.54-1.39)
Hepatic steatosis	20	1631	619	40.09	[33.64-46.90]		
No hepatic steatosis	20	4601	2031	42.25	[34.89-49.97]		
Significant fibrosis (≥stage 2)						0.28	0.68 (0.37-1.24)
Hepatic steatosis	13	1205	454	41.68	[29.69-54.73]		
No hepatic steatosis	13	3741	1774	51.32	[39.58-62.92]		
Advanced fibrosis (≥stage 3)						0.06	1.53 (0.89-2.64)
Hepatic steatosis	7	426	165	37.96	[30.53-46.00]		
No hepatic steatosis	7	860	257	27.12	[19.88-35.82]		
HS diagnostic method						0.62	
Liver biopsy	17	1267	479	39.56	[31.64-48.08]		
Controlled attenuation parameter	2	341	129	37.83	[32.84-43.10]		
Ultrasound	1	23	11	47.83	[28.80-67.51]		

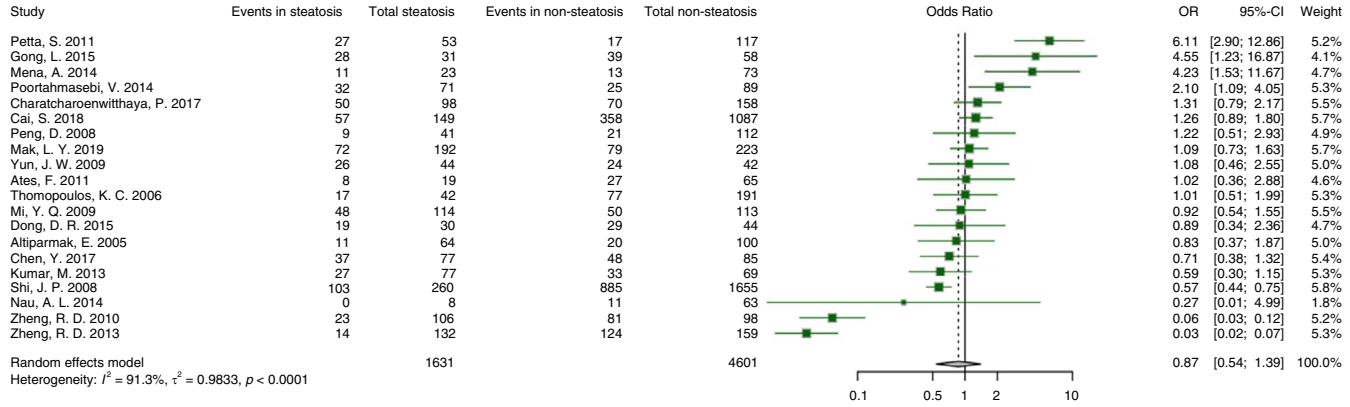

FIGURE 2 Association between hepatic steatosis and fibrosis (stage ≥2 or ≥3) among chronic hepatitis B (CHB) patients

same method can render the data heterogeneous, resulting in high level of heterogeneity even in our subgroup analysis by diagnostic method of HS and data should be interpreted with caution. The prevalence of HS is also most likely underestimated by ultrasound, but liver biopsy is invasive and not practical for diagnosis of HS in routine clinical setting, though it is the gold standard. There are also limitations on the fibrosis assessment. Liver biopsy is the gold standard for both HS and fibrosis diagnosis but was used in only 38 studies. Transient elastography which was used in five studies, though reliable for the determination of cirrhosis, is less reliable in term of optimal cut-off for lesser fibrosis stages. Similarly, there is also lack of consensus on the optimal CAP cut-off for HS. Ultrasound, the most common modality used in the clinical diagnosis of HS, has its own limitation. However, diagnosis mode was not significantly associated with HS prevalence and majority of included studies were still based on histology. Furthermore, the cut-off values of age, HBV DNA and study year categories were based on mean or median values of included studies, which may not be meaningful as they were data-driven. Lastly, we did not have sufficient data to analyse the impact of various degree of HS especially in studies that used ultrasound for diagnosis, as ultrasound is insensitive for detection of mild HS or grade the severity of HS.

However, while our study cannot provide data for the specific contribution of HS to inflammation and/or fibrosis in CHB patients, our study results provided pooled data from a large number of patients and studies to inform practitioners and future researchers of the high prevalence of HS among CHB patients and importantly the lack of association between the presence of HS and increased fibrosis in CHB patients, an intriguing finding that requires investigation. Indeed, a recent study of CHB patients with biopsy-proven NASH found no significant differences in poor clinical outcomes between CHB patients with NASH compared to those without NASH, but it was advanced fibrosis that predicted poor outcomes, regardless of the presence of NASH.[6] The negative association between HS and HBV DNA levels as well as aminotransferase levels and associated mechanism should also deserve additional attention. Prior animal studies have suggested that the presence of HS may alter the hepatic environment leading to decreased viral replication and it is likely that the associated HBV DNA level can lead to lower inflammatory activity in the liver leading to lower serum aminotransferase levels.[12,40,41]

In summary, in this systematic review and meta-analysis, we confirmed that concurrent HS was present in about one-third of the CHB population, with positive association with age, male gender, diabetes and metabolic syndrome, and negative association with HBeAg and HBV DNA levels. Notably, the presence of HS did not appear to be associated with higher prevalence of significant fibrosis. We found that approximately 40% of the study population had fibrosis (F2-F4) regardless of the presence of HS. Further studies are needed to evaluate the effect of HS on long-term complications such as HCC, hepatic decompensation and mortality. Additional studies are also needed to investigate the mechanism for the negative association between HS and HBV DNA levels as well as lack of association between HS and significant fibrosis in CHB.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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