



REVIEW

Impact of Metabolic Dysfunction-Associated Fatty Liver Disease of Varying Severity on Antiviral Treatment Outcomes and Clinical Prognosis in Patients with Chronic Hepatitis B: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: The coexistence of hepatitis B virus (HBV) infection and metabolic dysfunction-associated fatty liver disease (MAFLD) is becoming increasingly common. The bidirectional interaction between persistent HBV infection and lipotoxicity may influence the progression of the disease. However, to date, there has been a lack of meta-analyses that stratify this dual-disease population based on the severity of MAFLD.

Methods: This study was conducted in accordance with the PRISMA guidelines. Relevant literature on chronic hepatitis B (CHB) coexisting with MAFLD, published in Chinese and English databases from inception to January 6, 2025, was systematically retrieved. A meta-analysis was performed to evaluate the impact of MAFLD of

varying severity on the efficacy of antiviral therapy and clinical outcomes in patients with CHB.

Results: A total of 24 studies were included, among which seven investigated the impact of MAFLD severity on antiviral treatment efficacy, and 17 explored the influence of MAFLD on clinical outcomes in CHB. The meta-analysis revealed the following:

- HBeAg seroclearance rate: For the mild MAFLD group versus the CHB-only group, the odds ratio (OR) was 0.62; for the moderate-to-severe MAFLD group versus the CHB-only group, OR=0.37, indicating a more pronounced negative impact of moderate-to-severe MAFLD on HBeAg seroconversion.
- HBsAg seroclearance rate: For the mild MAFLD group versus the CHB-only group, OR=0.43; for the moderate-to-severe MAFLD group versus the CHB-only group, OR=0.20, further supporting the greater adverse effect of more severe MAFLD on HBsAg seroclearance.
- Incidence of hepatocellular carcinoma (HCC): For the CHB combined with MAFLD group versus the CHB-only group, OR=1.77, demonstrating a markedly increased risk of HCC development in the CHB combined with MAFLD group compared to the CHB-only group.

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Conclusions: This study is the first to systematically examine the complex relationship between CHB and MAFLD from the perspective of hepatic steatosis severity stratification. CHB combined with moderate-to-severe MAFLD is associated with HBsAg/HBeAg seroclearance rate and the likelihood of achieving functional cure, suggesting that MAFLD may exert a potentially beneficial effect on antiviral therapy. However, MAFLD is also significantly associated with an increased risk of HCC, potentially accelerating hepatic carcinogenesis through lipotoxic pathways.

Keywords: Degree of severity; Hepatitis B; Chronic; Metabolic dysfunction-associated steatotic liver disease; Meta-analysis

Key Summary Points

The coexistence of chronic hepatitis B (CHB) and metabolic dysfunction-associated fatty liver disease (MAFLD) is increasingly observed in clinical settings, accompanied by significant economic burden and unmet clinical needs. However, systematic analyses stratified by the severity of MAFLD are currently lacking.

This study aimed to assess how varying severity of MAFLD affects antiviral treatment efficacy and clinical outcomes in patients with CHB, with a particular focus on how MAFLD severity influences therapeutic response and disease progression.

Coexistence of CHB and moderate-to-severe MAFLD is associated with reduced rates of HBsAg and HBeAg clearance but is also linked to a significantly higher risk of hepatocellular carcinoma (HCC). This suggests a dual-pathogenic mechanism of MAFLD in the context of CHB.

These results highlight the urgent need for stratified metabolic interventions, enhanced HCC surveillance, and personalized antiviral treatment strategies. Future research should aim to construct a “severity–effect” dynamic model linking hepatic steatosis to antiviral efficacy, in order to precisely define the metabolic–immune thresholds that determine MAFLD’s impact on CHB therapy. This would ultimately improve prognoses for patients with CHB with coexisting MAFLD and guide future research directions.

INTRODUCTION

Chronic Hepatitis B (CHB) is a long-term liver disease caused by the Hepatitis B Virus (HBV). As a hepatotropic DNA virus, HBV infection is globally widespread. Studies have shown [1, 2] that approximately 296 million people worldwide are affected by CHB, and as of 2022, there were about 79.7 million chronic HBV infections in China, accounting for 31.5% of the global total [3]. The virus possesses complex structural characteristics, the ability to persist via covalently closed circular DNA (cccDNA), multiple immune evasion strategies, and regulatory effects on host epigenetics [4], forming the biological foundation for its high infectivity, chronicity, and carcinogenicity. These features not only contribute to the progressive pathogenesis of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) but also present major obstacles to achieving complete cure with current antiviral treatments. Due to factors such as insulin resistance, genetic predisposition, and metabolic disorders, the prevalence of CHB combined with metabolic dysfunction-associated steatotic liver disease (MAFLD) continues to rise. In recent years, international organizations have proposed renaming non-alcoholic fatty liver disease (NAFLD) to MAFLD. Research has found [5] that the differences between MAFLD and NAFLD are minimal, and therefore, findings from studies conducted under the NAFLD definition remain valid for MAFLD. Reports indicate that the global incidence of CHB combined with MAFLD ranges

from 14 to 70% [6]. The interaction between CHB and MAFLD creates a unique pathophysiological environment in which persistent viral infection and lipotoxic injury mutually reinforce each other, resulting in a “double-edged sword” effect.

As MAFLD progresses, the influence of viral factors in patients with CHB gradually weakens, while the role of metabolic factors increases. Studies have shown [7, 8] that hepatic steatosis is significantly associated with the risk of liver fibrosis progression. On the other hand, it has been found [9] that cellular steatosis inhibits HBV secretion, promotes HBsAg seroclearance, and is associated with better outcomes, such as lower risks of HCC, cirrhosis, and mortality [10]. However, stratified meta-analyses based on the severity of MAFLD are still lacking, and current guidelines do not provide evidence-based recommendations on monitoring frequency or treatment adjustment for patients with this dual disease profile. Therefore, this study aims to conduct a systematic review and meta-analysis to evaluate the effects of varying degrees of MAFLD on antiviral efficacy and clinical outcomes in patients with CHB. The goal is to identify key thresholds at which MAFLD affects antiviral treatment, thereby providing an evidence-based basis for precision-stratified management of patients with CHB with coexisting MAFLD.

METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol has been registered in the PROSPERO database (registration number: CRD420250652601). This article is based on previously published studies and does not include any new research involving human participants or animals conducted by the authors.

Literature Search

A comprehensive computer-based search was conducted across the following databases: PubMed, Embase, Cochrane Library, Web of Science,

CNKI, Wanfang, VIP, Chinese Medical Journal, and the Chinese Biomedical Literature Database (CBM), covering the period from the inception of each database to January 6, 2025. The search strategy was constructed using the PICOS framework and optimized using a combination of Medical Subject Headings (MeSH) and free-text terms to maximize sensitivity and specificity. English search terms included: “chronic hepatitis B virus,” “Hepatitis B, Chronic,” “fatty liver,” “Non-alcoholic Fatty Liver Disease,” “Clinical Outcomes,” “liver fibrosis,” “Liver Cirrhosis,” “Liver Neoplasms,” “Liver failure,” “antiviral therapy,” “Nucleoside Analogues,” “Interferon,” and “Therapeutic.” Chinese search terms included: “chronic viral hepatitis B,” “Chronic hepatitis B,” “Hepatitis B, chronic,” “Hepatic steatosis,” “Nonalcoholic fatty liver disease,” “Metabolic fatty liver disease,” “Antiviral therapy,” “Clinical outcome,” “Prognosis,” “Hepatocellular carcinoma,” “Liver cirrhosis,” and “Liver fibrosis,”

Inclusion and Exclusion Criteria

The specific inclusion and exclusion criteria for the literature are detailed in Table 1.

Literature Selection and Data Extraction

Two researchers (Qianqian Zhu and Chengde Su) independently performed literature screening and data extraction and cross-checked the results. Any disagreements were resolved through discussion with a third researcher (Mingdan Li). After removing duplicate records, titles and abstracts were reviewed to exclude irrelevant studies, reviews, meta-analyses, conference abstracts, and other non-eligible articles. Full texts of the remaining studies were then assessed strictly based on the predefined inclusion and exclusion criteria to determine final eligibility. A standardized data extraction form was developed using Excel. Extracted data included: first author, publication year, country, study design, sample size, diagnostic methods. Study quality was assessed using the Newcastle–Ottawa Scale (NOS) and the Agency for Healthcare Research

Table 1 Inclusion and exclusion criteria for literature selection

Inclusion criteria	exclusion criteria
(1) Study population: Patients diagnosed with CHB combined with MAFLD according to clinical guidelines, aged > 18 years	(1) Review articles, meta-analyses, animal experiments, or conference abstracts
(2) Study grouping: Clear distinction between CHB + MAFLD group and CHB-only group	(2) Study population: Unclear disease diagnosis, co-infection with other hepatotropic viruses or HIV, pregnancy, or end-stage diseases
(3) Outcomes: Antiviral efficacy (HBV DNA suppression rate, ALT normalization rate, HBeAg/HBsAg seroclearance rate) or clinical outcomes (liver fibrosis, cirrhosis, hepatocellular carcinoma, mortality) HBeAg/HBsAg seroclearance: Undetectable levels in serum by standard assays HBV DNA suppression: HBV DNA < 10 ³ copies/ml ALT normalization: ALT < 40 U/l	(3) Low-quality studies: Studies with poor design, small sample size, or insufficient analysis of key data;
(4) Study design: Cohort studies, randomized controlled trials, case–control studies, or cross-sectional studies	(4) Duplicate publications: Excluding studies published more than once
(5) Language: Published in Chinese or English	

and Quality (AHRQ) criteria for cross-sectional studies.

Quality Assessment of Included Studies

Two researchers (Qianqian Zhu and Chengde Su) assessed the quality of the included studies using the NOS [11] and AHRQ [12] criteria. Discrepancies were resolved through consultation with a third researcher (Yali Xu). The NOS assesses three domains: study subject selection, intergroup comparability, and exposure factors, with a total score of 9. Studies scoring ≥ 6 points were considered high quality. The AHRQ tool includes 11 items, each answered as “yes,” “no,” or “unclear.” Responses were scored as 0 points (no/unclear) or 1 point (yes). Based on the total score, studies were classified as: low quality (0–3 points), moderate quality (4–7 points), or high quality (8–11 points).

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4, developed by the

Cochrane Collaboration (UK). For all outcome indicators, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated as effect size measures. Heterogeneity was assessed using the I^2 statistic. If $P \geq 0.1$ and $I^2 \leq 50\%$, no significant heterogeneity was assumed and a fixed-effect model was used. Otherwise, a random-effect model was applied. For indicators with significant heterogeneity, Egger’s test or Begg’s test was conducted using Stata version 18 (USA), with $P < 0.05$ considered statistically significant.

RESULTS

Literature Screening Process and Basic Characteristics of Included Studies

A total of 4867 articles were initially retrieved. After reviewing the titles, abstracts, and full texts, and applying the inclusion and exclusion criteria, 24 studies were finally included. Among them, 17 studies reported clinical outcome indicators [13–29], including 11 cohort studies [13, 14, 16–21, 25, 26, 29], five case–control

studies [22–24, 27, 28], and one cross-sectional study [15]. Seven studies reported antiviral efficacy indicators, all of which were cohort studies [30–36]. The literature screening process is

shown in Fig. 1, the basic characteristics of the included studies are shown in Table 2, and the criteria for classifying MASLD severity are presented in Table 3.

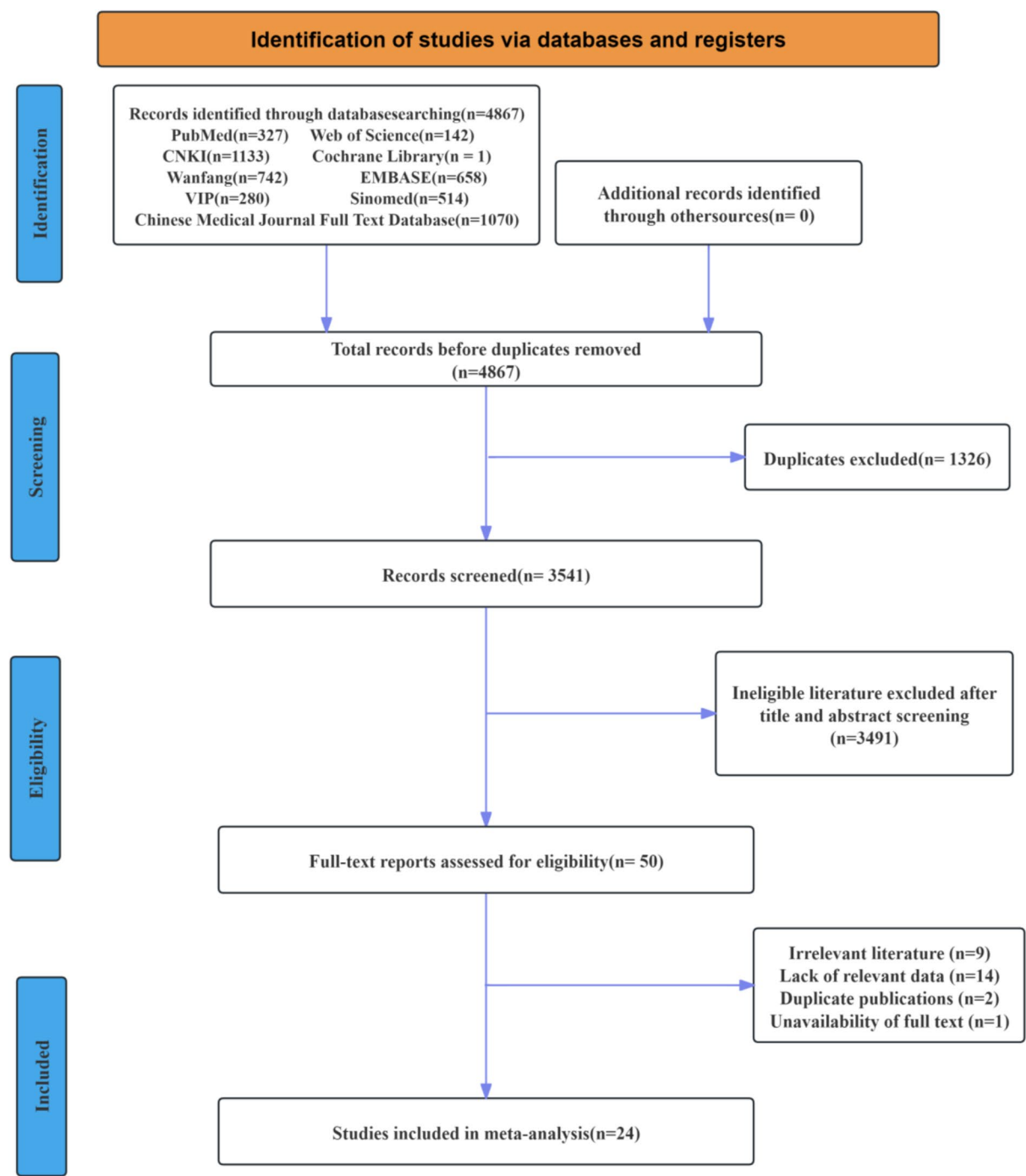


Fig. 1 Literature screening flowchart

Table 2 Basic characteristics of included studies

Author (year)	Location	Publi- cation language	Study	Sample size	FL diagnostics	Medication	Male (%)		Female (%)		NOS score
							CHB	CHB + FL	CHB	CHB + FL	
Zhang (2014) [36]	China	Chinese	PCS	341	Liver biopsy	Polyethylene gly- col interferons	52	87.22	48	12.78	8
Han (2021) [31]	China	Chinese	PCS	180	NA	Adefovir dipivoxil	54.44	51.11	45.56	48.89	8
Yu (2019) [35]	China	Chinese	PCS	102	Liver biopsy	Entecavir	58.82	54.9	41.18	45.1	7
Lu (2014) [32]	China	Chinese	RCS	330	Liver biopsy	Polyethylene gly- col interferons	52.44	87.5	47.56	12.5	8
Yu Z. (2019) [34]	China	Chinese	PCS	102	Ultrasound	Polyethylene gly- col interferons	NA	NA	NA	NA	8
Wu (2017) [33]	China	Chinese	PCS	164	Liver biopsy	Entecavir	43.8	60	56.2	40	8
Dai (2023) [30]	China	Chinese	PCS	208	Ultrasound	Entecavir	67.28	70.37	32.72	29.63	8
Ko, H. H. (2022) [15]	Canada	English	CSS	1178	Ultrasound	NA	52.5	61.7	47.5	38.3	6 (AHRQ)
Huang (2023) [20]	China, Taiwan	English	PCS	10,546	Ultrasound	NA	47	68	53	32	8
Choi (2021) [14]	Canada	English	PCS	1089	Liver biopsy	NA	62.9	80.5	37.1	19.5	8
Peleg (2019) [19]	Israeli	English	RCS	524	Liver biopsy	NA	58.9	61.1	41.1	38.9	8
Ou 2024 [28]	China	Chinese	CCS	150	Liver biopsy	NA	NA	NA	NA	NA	7
Lü 2024 [27]	China	Chinese	CCS	299	Liver biopsy	NA	50.6	71.76	49.4	28.24	7
Chen 2021 [23]	China	Chinese	CCS	146	Liver biopsy	NA	95.3	87.4	4.7	12.6	7
Xie 2018 [37]	China	Chinese	RCS	240	Liver biopsy	NA	66.67	68.18	33.33	31.82	7
Li 2022 [25]	China	Chinese	PCS	253	Ultrasound	NA	71.3	76	28.7	24	9
Jiang 2017 [24]	China	Chinese	CCS	1036	Liver biopsy	NA	81.5	61	18.5	39	8
Chen 2023 [22]	China	Chinese	CCS	364	Liver biopsy	NA	62.3	80	37.7	20	8

Table 2 continued

Author (year)	Location	Publi- cation language	Study	Sample size	FL diagnostics	Medication	Male (%)		Female (%)		NOS score
							CHB	CHB+FL	CHB	CHB+FL	
Liu 2022 [26]	China	Chinese	PCS	215	Liver biopsy	NA	66.67	78.22	33.33	21.78	8
Lee (2018) [21]	Korea	English	PCS	321	Liver biopsy	NA	58.2	71.4	41.8	28.6	8
van Kleef (2021) [17]	Canada	English	RCS	1076	Liver biopsy	NA	60.3	80.1	39.7	19.9	8
Yun (2022) [16]	Korea	English	RCS	197,346	Fatty liver index ≥ 30	NA	45.8	77.6	54.2	22.4	8
Lim (2020) [13]	Singaporean	English	RCS	289	Liver biopsy	NA	65.4	76.2	34.6	23.8	8
Yu (2022) [18]	China, Taiwan	English	PCS	1453	Ultrasound	NA	100	100	0	0	8

PCS prospective cohort study, RCS retrospective cohort study, CSS cross-sectional study

Quality Assessment of Included Studies

Among the 24 included studies, the cross-sectional study [15] received a score of 6 on the AHRQ scale. The remaining 23 studies [13, 14, 16–36] scored no less than 7 on the NOS scale, indicating high-quality literature, as shown in Table 2.

Meta-analysis Results

Subgroup Analysis by MAFLD Severity: No Association Between HBV-DNA Suppression Rate or ALT Normalization Rate and MAFLD Severity

Six studies [30–34, 36] reported HBV-DNA suppression rates. A subgroup analysis based on MAFLD severity (mild vs. moderate-to-severe) included a total of 1325 patients—907 in the CHB combined with MAFLD group and 418 in the CHB-only group. The results are shown in Fig. 2. The pooled OR for HBV-DNA suppression rate was 0.66 (95% CI 0.44–1.00, $I^2=70\%$, $P=0.05$), suggesting that the suppression rate in the CHB combined with MAFLD group was 0.52 times that of the CHB-only group. A random-effects model was used due to significant heterogeneity ($I^2>50\%$). There were no statistically significant differences between the CHB combined with mild MAFLD subgroup and CHB combined with moderate-to-severe MAFLD subgroup ($P=0.35$ and $P=0.09$, respectively).

Six studies [30–33] reported ALT normalization rates. Subgroup analysis by MAFLD severity (mild vs. moderate-to-severe) included 1305 patients—883 in the CHB combined with MAFLD group and 442 in the CHB-only group. The results are shown in Fig. 3. A random-effects model was used due to significant heterogeneity ($I^2>50\%$). No statistically significant differences were found between the CHB combined with mild MAFLD subgroup versus the CHB-only group ($P=0.48$), or between the CHB combined with moderate-to-severe MAFLD subgroup versus the CHB-only group ($P=0.31$).

Table 3 MASLD severity classification criteria

Author (year)	Hepatitis B diagnostic criteria	Diagnostic criteria for fatty liver	Basis of grading	Follow-up time
Zhang (2014) [36]	Diagnostic criteria for chronic hepatitis B (2010 version) [38]	Guidelines for the diagnosis and treatment of non-alcoholic fatty liver disease [39]	Mild steatosis: 5–30% of hepatocyte steatosis in the liver lobules; moderate-to-severe steatosis > 30% of hepatocyte steatosis in the liver lobules	48 weeks
Han (2021) [31]	Diagnostic criteria for CHB in the viral hepatitis control program 2000	2010 Guidelines for the management of nonalcoholic fatty liver disease [39]	NA	24 weeks
Yu (2019) [35]	Diagnostic criteria for chronic hepatitis B (2010 version) [38]	2010 Guidelines for the Management of Nonalcoholic Fatty Liver Disease [39]	Mild steatosis: 5–30% of hepatocyte steatosis in the liver lobules; moderate-to-severe steatosis: > 30% of hepatocyte steatosis in the liver lobules	48 weeks
Lu (2014) [32]	Diagnostic criteria in the 2005 guidelines for the management of chronic hepatitis B [40]	2005 Guidelines for the diagnosis and treatment of non-alcoholic fatty liver disease [41]	Mild: 25% to 50% cellular steatosis; severe: > 50% cellular steatosis	52 weeks
Yu (2019) [34]	Diagnostic criteria for chronic hepatitis B (2010 version) [38]	NA	NA	26 weeks
Wu (2017) [33]	Diagnostic criteria for chronic Hepatitis B (2010 version) [38]	2010 Guidelines for the Management of Nonalcoholic Fatty Liver Disease [39]	Mild steatosis: 5–30% of hepatocyte steatosis in the liver lobules; moderate-to-severe steatosis: > 30% of hepatocyte steatosis in the liver lobules	48 weeks
Dai (2023) [30]	Guidelines for the management of chronic hepatitis B (2019 Edition) criteria [42]	Guidelines for the prevention and treatment of non-alcoholic fatty liver disease (2018 Edition) [43]	Mild: 238 ≤ CAP < 259, corresponding to 11–33% of steatosis Moderate: 259 ≤ CAP < 292, corresponding to 34–66% of steatosis Severe: CAP ≥ 292, corresponding to ≥ 67% steatosis	48 weeks

CAP controlled attenuation parameter

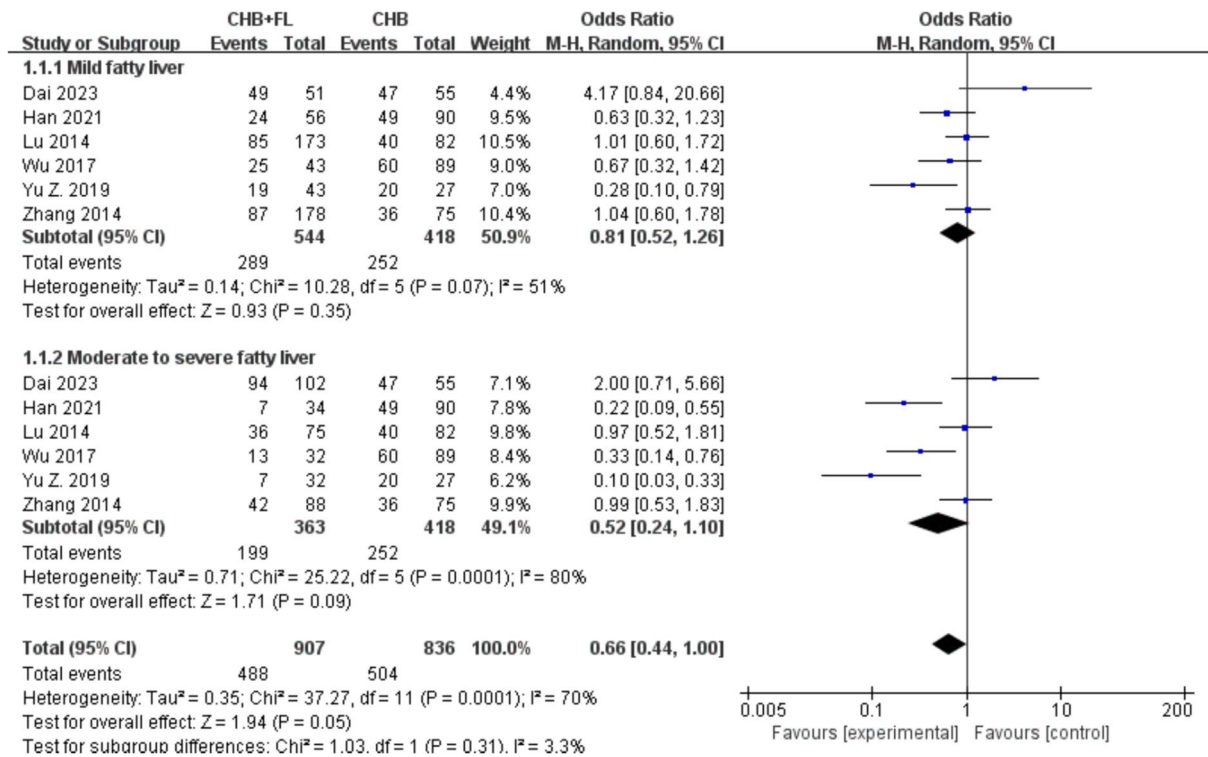


Fig. 2 Subgroup analysis of HBV DNA suppression rate based on MASLD severity. *CHB + FL* CHB combined with MAFLD group (intervention group); *CHB* CHB-only group (control group)

**Subgroup Analysis by MAFLD Severity:
Significantly Higher HBeAg Seroclearance Rate
in CHB Combined with Moderate-to-Severe
MAFLD Group**

Six studies [31–36] reported HBeAg seroclearance rates. A subgroup analysis based on MAFLD severity (mild vs. moderate-to-severe) included a total of 1219 patients—805 in the CHB combined with MAFLD group and 414 in the CHB-only group. The results are shown in Fig. 4. Since a lower OR value indicates better improvement in the experimental group versus controls, the analysis revealed: CHB combined with moderate-to-severe MAFLD showed significantly superior HBeAg seroclearance (OR 0.48, 95% CI 0.34–0.66, $P < 0.00001$) compared to CHB combined with mild MAFLD (OR 0.66, 95% CI 0.50–0.87, $P = 0.004$). A random-effects model was applied due to substantial heterogeneity ($I^2 > 50\%$). The pooled analysis demonstrated that, despite moderate heterogeneity ($I^2 = 64\%$), the CHB combined with MAFLD group had a

significantly higher HBeAg seroclearance rate than the CHB-only group (OR 0.57, 95% CI 0.46–0.71, $P < 0.00001$).

**Subgroup Analysis by MAFLD Severity:
Significantly Higher HBsAg Seroclearance Rate
in CHB Combined with Moderate-to-Severe
MAFLD Group**

Three studies [31, 34, 35] reported HBsAg seroclearance rates. A subgroup analysis based on MAFLD severity (mild vs. moderate-to-severe) included a total of 384 patients—216 in the CHB combined with MAFLD group and 168 in the CHB-only group. The results are shown in Fig. 5. A fixed-effect model was employed due to low heterogeneity ($I^2 < 50\%$). The HBsAg seroclearance rate in the CHB combined with moderate-to-severe MAFLD subgroup (OR 0.20, 95% CI 0.11–0.36, $P < 0.00001$) was significantly better than that in the CHB combined with mild MAFLD subgroup (OR 0.43, 95% CI 0.26–0.70, $P = 0.0006$). Overall, the

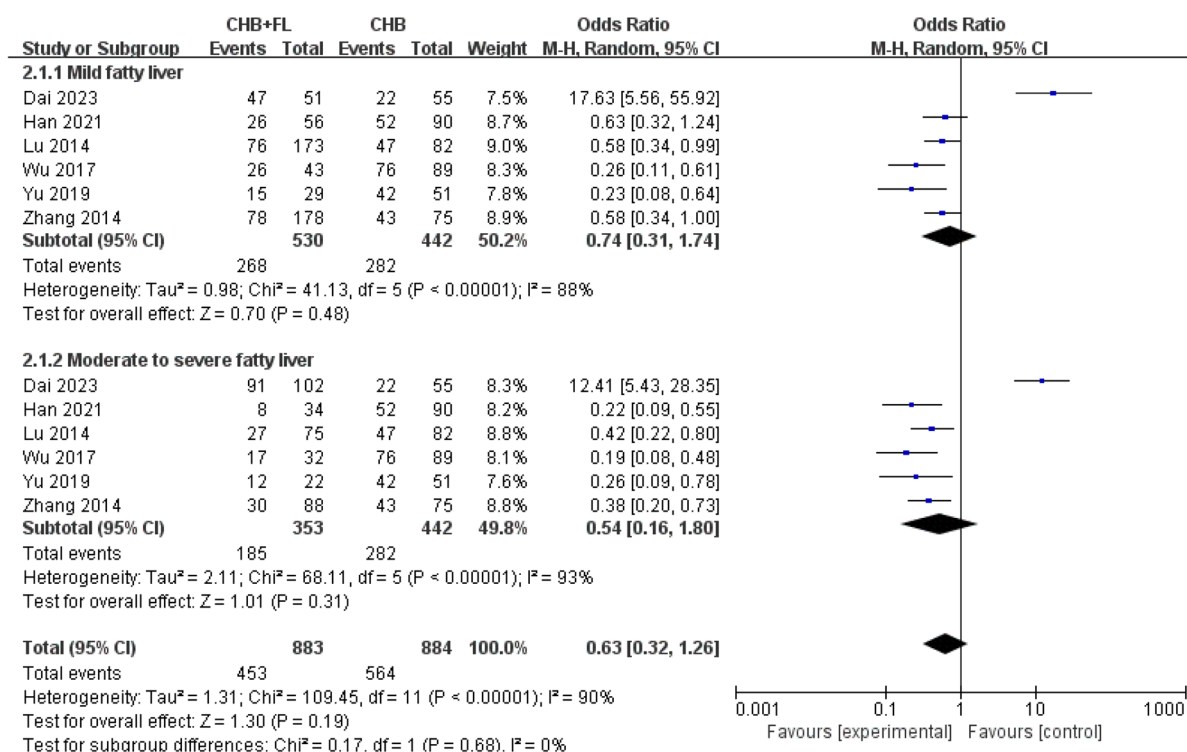


Fig. 3 Subgroup analysis of ALT normalization rate based on MASLD severity. *CHB + FL* CHB combined with MAFLD group (intervention group), *CHB* CHB-only group (control group)

CHB combined with MAFLD group exhibited a significantly higher HBsAg seroclearance rate than the CHB-only group (OR 0.31, 95% CI 0.21–0.46, $P < 0.00001$).

Increased Risk of HCC in CHB Combined with MAFLD Group

Eleven studies [13–18, 20–22, 26] reported on the incidence of hepatocellular carcinoma (HCC), involving a total of 213,870 patients—70,499 in the CHB combined with MAFLD group and 143,902 in the CHB-only group. The results are shown in Fig. 6. A random-effects model was applied due to high heterogeneity ($I^2 = 84\%$). The analysis indicated that patients with CHB with MAFLD had a 1.77-fold higher risk of developing HCC compared to CHB-only patients (OR 1.77, 95% CI 1.13–2.77, $P = 0.01$), suggesting that MAFLD may serve as a pro-carcinogenic factor in patients with CHB, significantly increasing HCC risk.

No Significant Increase in Mortality, Liver Fibrosis Incidence, or Liver Cirrhosis Incidence in Patients with CHB and MAFLD

Two studies [14, 18] reported mortality rates, as shown in Fig. 7. There was no significant difference in mortality between the CHB combined with MAFLD group and the CHB-only group (OR 0.98, 95% CI 0.42–2.31, $P > 0.05$). Six studies [22–24, 27–29] reported liver fibrosis incidence, as shown in Fig. 8, with no significant difference between the CHB combined with MAFLD group and the CHB-only group (OR 1.01, 95% CI 0.54–1.89, $P > 0.05$). Four studies [15, 18, 25, 26] reported liver cirrhosis incidence, as shown in Fig. 9, with no significant difference between the CHB combined with MAFLD group and the CHB-only group (OR 1.08, 95% CI 0.36–3.28, $P > 0.05$). In summary, the presence of MAFLD did not significantly alter mortality, liver fibrosis progression, or cirrhosis risk in patients with CHB.

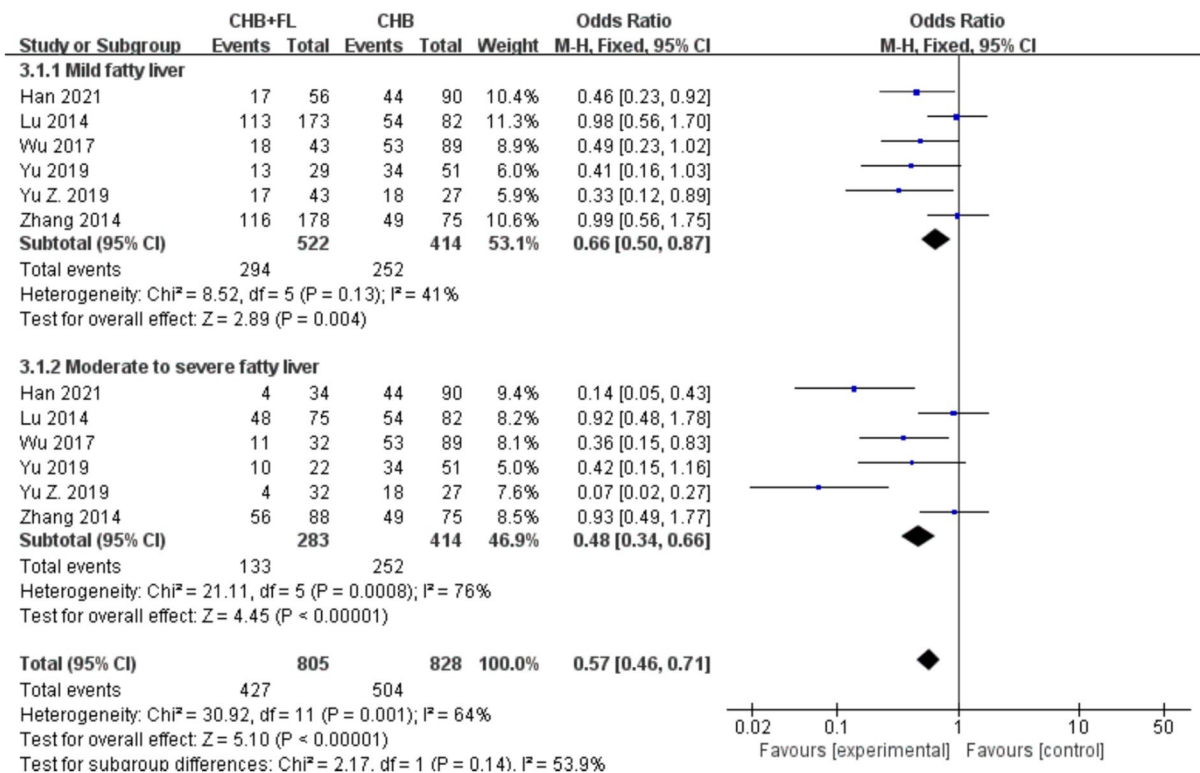


Fig. 4 Subgroup analysis of HBsAg seroclearance rate based on MASLD severity. *CHB+FL* CHB combined with MAFLD group (intervention group); *CHB* CHB-only group (control group)

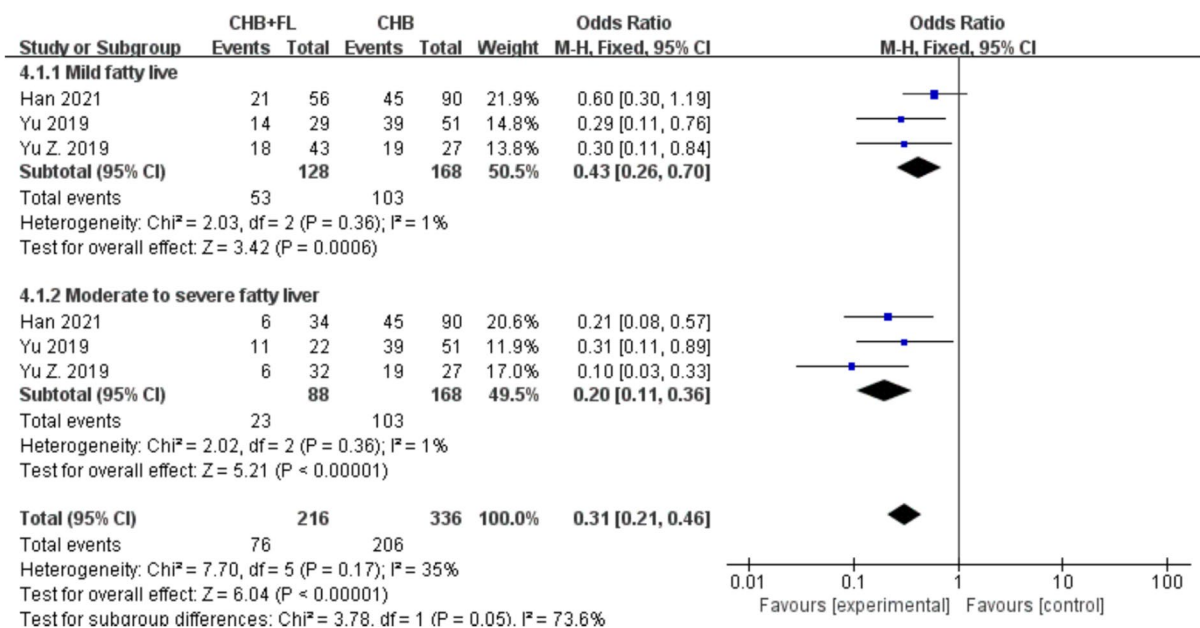


Fig. 5 Subgroup analysis of HBsAg seroclearance rate based on MASLD severity. *CHB+FL* CHB combined with MAFLD group (intervention group); *CHB* CHB-only group (control group)

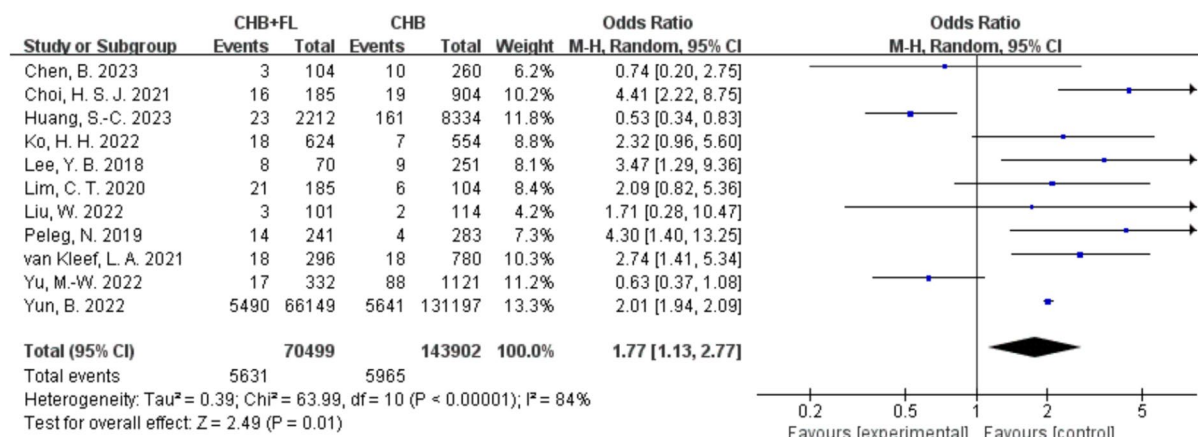


Fig. 6 Clinical outcome—incidence of hepatocellular carcinoma (HCC). *CHB+FL* CHB combined with MAFLD group (intervention group); *CHB* CHB-only group (control group)

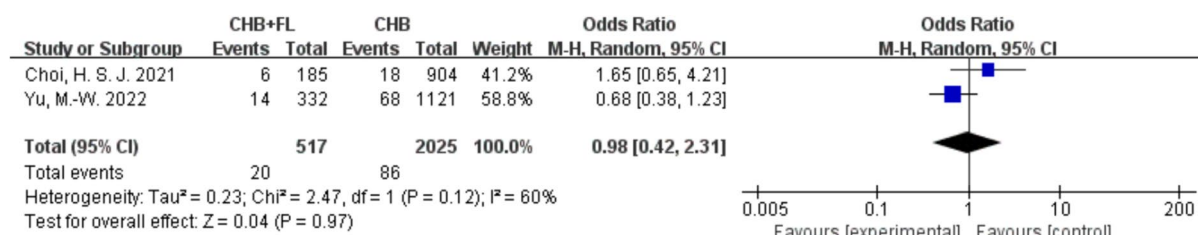


Fig. 7 Clinical outcome—mortality rate. *CHB+FL* CHB combined with MAFLD group (intervention group), *CHB* CHB-only group (control group)

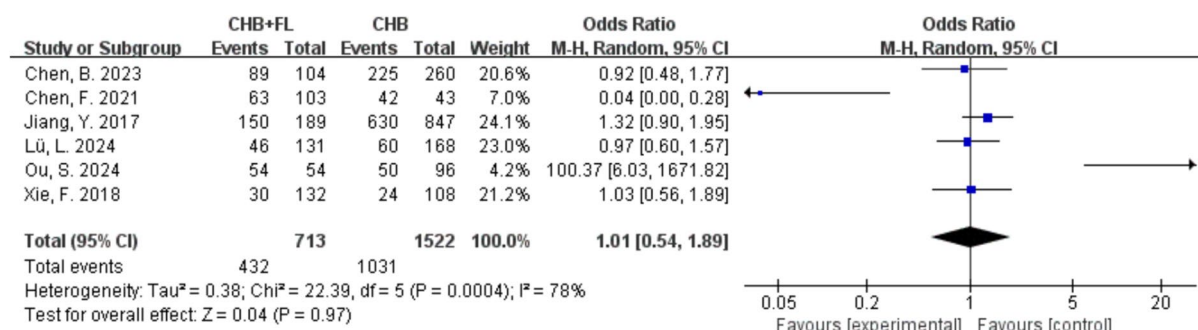


Fig. 8 Clinical outcome—incidence of liver fibrosis. *CHB+FL* CHB combined with MAFLD group (intervention group), *CHB* CHB-only group (control group)

Publication Bias

Egger's test was performed using HCC incidence (with > 10 included studies) as the outcome

indicator. The results showed a P value of 0.53 for HCC incidence, suggesting a low probability of publication bias. Funnel plots for HBeAg and HBsAg seroclearance rates showed roughly symmetrical distributions on both sides of the

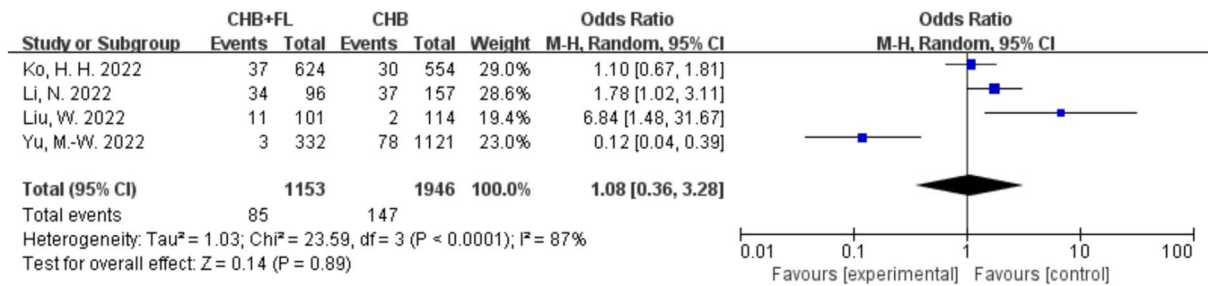


Fig. 9 Clinical outcome—incidence of cirrhosis. *CHB + FL* CHB combined with MAFLD group (intervention group); *CHB* CHB-only group (control group)

vertical line, and Begg’s test yielded $P > 0.05$, again indicating low likelihood of publication bias. For HBV-DNA suppression rate, ALT normalization rate, and liver fibrosis incidence, Begg’s test also showed $P > 0.05$, suggesting minimal publication bias. For other outcome indicators, due to the small number of studies, publication bias could not be formally assessed. Future research should expand sample sizes to enable more comprehensive evaluation of publication bias.

DISCUSSION

This study, through a meta-analysis, reveals the complex interaction patterns between CHB and the stratified severity of MAFLD, filling a gap in previous research regarding the grading of MAFLD. The results show that patients with CHB combined with MAFLD exhibit both beneficial and adverse clinical outcomes in terms of antiviral efficacy and adverse clinical outcome indicators. While moderate-to-severe MAFLD may enhance the HBsAg seroclearance rate, it also significantly increases the risk of HCC, indicating a paradoxical “immune activation-carcinogenic transformation” effect. This suggests that MAFLD may positively influence certain aspects of antiviral therapy but does not necessarily improve all therapeutic indicators. Therefore, MAFLD may exert dual influences during the treatment of patients with CHB, warranting further in-depth research to elucidate its specific roles and underlying mechanisms.

The relationship between HBV infection and MAFLD remains an actively explored and debated area. Several studies [44, 45] have reported a significant inverse correlation between hepatic steatosis and viral load; however, the severity of steatosis was not clearly defined in these studies, thereby limiting a comprehensive understanding of MAFLD’s impact on antiviral efficacy in HBV infection. Against this backdrop, we stratified patients based on the severity of steatosis into the CHB combined with mild MAFLD subgroup and the CHB combined with moderate-to-severe MAFLD subgroup, to further investigate the effect of MAFLD on antiviral treatment outcomes in patients with CHB. Our findings revealed that patients in the CHB combined with moderate-to-severe MAFLD subgroup had better antiviral responses (HBeAg and HBsAg seroclearance rates) than those in the CHB combined with mild MAFLD subgroup. A case–control study [46] similarly reported that the prevalence of moderate-to-severe hepatic steatosis was significantly higher in patients who achieved HBsAg clearance (the HBsAg seroclearance group) compared to chronic HBV carriers (the CHB group), with moderate and severe steatosis increasing the likelihood of HBsAg clearance by 3.2-fold and 3.9-fold, respectively. This may be due to hepatic steatosis inducing oxidative stress and remodeling the hepatic immune microenvironment, thereby activating immune function via stimulation of envelope-specific CD4 + T cells and promoting B-cell activation for anti-HBs production, which indirectly enhances antiviral efficacy [47]. Alternatively, fatty acids may activate the Toll-like receptor 4 (TLR4) signaling pathway, enhancing hepatic immune

responses. Upregulation of TLR4 can promote the restoration of innate immunity and activate adaptive immune cells, thereby accelerating HBsAg/HBV DNA clearance [48, 49]. However, a meta-analysis by Li Jie et al. [50] evaluating antiviral treatment duration showed no statistically significant differences in complete viral suppression rate or HBeAg seroclearance rate at 48 and 96 weeks between patients with CHB with and without fatty liver disease.

Although these studies have shed light on some of the mechanisms underlying the interaction between CHB and MAFLD, the two diseases involve multiple pathophysiological pathways, and the current body of evidence has yet to fully elucidate the essential characteristics and causal relationships of their interaction. Future research should aim to establish a dynamic “severity-effect” correlation model between hepatic steatosis and antiviral efficacy to precisely define the metabolic-immune thresholds at which MAFLD impacts CHB treatment. To achieve this, multi-modal systems biology approaches may be employed, including mass spectrometry imaging-based analysis of spatial lipid subtypes in hepatocytes [51], single-cell transcriptomics to profile dynamic immune cell subpopulations associated with the TLR4 pathway [52], and chromatin conformation capture techniques to evaluate epigenetic modifications of HBV cccDNA [53]. Additionally, feature fusion using machine learning-driven graph neural networks, combined with longitudinal antiviral efficacy data, could support the construction of multi-parameter predictive models to identify critical thresholds of MAFLD’s impact on antiviral efficacy. Ultimately, an adaptive clinical trial design, incorporating causal forest algorithms to quantify the synergistic effects of metabolic interventions, may drive the clinical translation of precision medicine research.

Although studies suggest that MAFLD may have positive effects on patients with CHB, long-term follow-up indicates a possible increase in HCC risk, which poses a serious threat to patient health and increases the medical burden, highlighting the need for further research and proactive intervention [54, 55]. Our study, by integrating data from multiple regions, found that the presence of MAFLD significantly increases

the risk of HCC in patients with CHB. Currently, the mechanisms by which MAFLD contributes to CHB-related HCC remain unclear. A potential explanation involves the synergistic effects of inflammatory responses, oxidative stress, and lipid metabolism disorders under comorbid conditions. A study [56] showed that the HBV-encoded X protein (HBx) can upregulate fatty acid transport protein 2 (FATP2), activating the FATP2-ACSL1 and FATP2-PPAR γ signaling axes, thereby promoting excessive lipid accumulation in the liver. Further studies [57] have shown that the high-lipid microenvironment in the liver exerts a dual effect on CHB. On one hand, lipid accumulation induces the expansion of regulatory T cells (Tregs) and activates oncogenic pathways such as PI3K/AKT/mTOR, thereby indirectly accelerating the development of HCC. On the other hand, lipid metabolic products directly interfere with the HBV life cycle: saturated fatty acids stabilize the HBx protein by inhibiting its proteasomal degradation, thereby enhancing viral transcriptional activity; cholesterol, as an essential component of the viral envelope, promotes viral particle assembly and secretion; and lipid metabolic reprogramming mediated by ACSL1 suppresses HBsAg expression, weakening host immune surveillance and ultimately exacerbating HBV immune evasion and persistent infection. These mechanisms suggest that targeting key regulators of lipid metabolism (e.g., FAS, ACSL1) may enable dual “metabolic-viral” intervention, providing a novel approach for the combined treatment of CHB and MAFLD.

In the context of CHB combined with MAFLD, MAFLD may promote HBV integration through oxidative stress, metabolic dysregulation, remodeling of the inflammatory microenvironment, and alterations in virus-host interactions [4], thereby independently increasing the risk of HCC via integration-driven carcinogenic pathways, without significantly elevating cirrhosis incidence. Although direct studies on how MAFLD regulates HBV integration are currently lacking, this finding offers a conceptual basis for the precise management of HBV infection associated with MAFLD. Future research should further explore synergistic strategies involving metabolic intervention and antiviral therapy to block the integration-carcinogenesis cascade

and improve patient prognosis. Evidence suggests [58] that liver fibrosis plays a critical role in the transition from autoimmune liver disease to HCC, with dynamic changes in gene regulatory networks across progression stages. Similar molecular mechanisms may also exist in the progression of CHB combined with MAFLD. Therefore, mapping the CHB phenotype based on MAFLD severity could not only help clarify phenotypic changes such as serologic conversion but also reveal, at a multi-omics level, how MAFLD influences HBV infection and HCC development, offering new perspectives and potential targets for clinical treatment. In clinical practice, enhanced HCC surveillance is recommended for patients with CHB with concurrent MAFLD, including shortening the intervals for ultrasound and Alpha-Fetoprotein (AFP) testing. Although some studies have proposed combination strategies involving antiviral therapy and metabolic management [59], and certain clinical trials have shown promise in improving liver function and reducing fat accumulation [60], there is still no consensus on personalized treatment plans, and a lack of precision treatment guidelines based on patients' genetic backgrounds and disease states. Additionally, it is necessary to further explore the potential role of metabolic interventions (e.g., weight loss and improved insulin sensitivity) in reducing liver cancer risk.

One of the strengths of this study lies in its large sample size and multi-regional design, which incorporates a substantial number of cases and considers data from multiple regions, thereby enhancing the generalizability and reliability of the conclusions. Uniquely, although many studies have examined the impact of disease duration on CHB outcomes, studies stratifying by MAFLD severity remain rare. This study innovatively stratified patients by the severity of MAFLD, which allows for a more precise evaluation of how different degrees of MAFLD affect antiviral efficacy and other outcomes in patients with CHB, offering more nuanced clinical insights.

This study also has several limitations. First, because China has the largest HBV-infected population globally [1], the proportion of Chinese samples is relatively high, and the genetic

background [61] (e.g., HBV genotype distribution) of the Chinese population may differ from that of other regions, potentially influencing the relationship between fatty liver and CHB. In addition, the included studies span a wide time period (2014–2024), during which diagnostic criteria, treatment guidelines, and clinical practices for CHB and fatty liver have undergone significant changes. Such temporal heterogeneity may affect the comparability of outcome indicators and increase heterogeneity in conclusions. Finally, the absence of individual-level data (e.g., baseline BMI, comorbid diabetes, etc.) limited our ability to control for metabolic factors and assess confounding effects, which may have increased variability in the results.

CONCLUSIONS

This study is the first to systematically reveal the complex association between CHB and MAFLD from the perspective of stratified severity of hepatic steatosis. CHB combined with moderate-to-severe MAFLD is associated with HBsAg/HBeAg seroclearance rate and the likelihood of achieving functional cure, suggesting that MAFLD may exert a potentially beneficial effect on antiviral therapy. However, MAFLD is also significantly associated with an increased risk of HCC, potentially accelerating hepatic carcinogenesis through lipotoxic pathways. This paradox underscores the complexity of metabolic–viral interactions and highlights the clinical need for an integrated “graded intervention–dynamic monitoring” management strategy. Future studies should incorporate multi-omics data and artificial intelligence technologies to develop precision treatment models based on dynamic changes in hepatic steatosis and genetic features, ultimately achieving personalized management of CHB–MAFLD comorbidity.

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Xu: Writing-review & editing, designed figures, Methodology, Formal analysis. Qian Liu: Data curation. Ying Zhang: designed figures. Xinyi Zhang: Visualization, Provision of materials. Qiuxiang Li, Huajun Wang: performed the quality assessment. Yawen Luo: Writing-review & editing. Ping Yang: critically reviewed and revised the manuscript. All authors read and approved of the final manuscript.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Qianqian Zhu: Chengde Su: Mingdan Li: Yali Xu, Qian Liu, Ying Zhang, Xinyi Zhang, Qiuxiang Li, Huajun Wang, Yawen Luo, Yawen Luo, Ping Yang declare that they have no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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