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SYSTEMATIC REVIEWS

Low level of hepatitis B viremia is associated with increased risk of hepatocellular carcinoma in compensated cirrhotic patients

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Abstract

BACKGROUND

Whether patients with compensated cirrhosis and low-level viremia (LLV) of hepatitis B should receive antiviral therapy (AVT) is still controversial, and published results are inconsistent.

AIM

To investigate the link between LLV in compensated cirrhosis and prognosis concerning hepatocellular carcinoma (HCC), decompensation, and liver-related events.

METHODS

The PubMed, EMBASE, and Cochrane Library databases were searched up to March 5, 2023. Outcomes of interest were assessed by pooled hazard ratios (HRs). The study was registered with PROSPERO (CRD42023405345).

RESULTS

Six cohort studies representing 3155 patients were included. Compared with patients with undetectable HBV DNA, patients with LLV was associated with increased risk of HCC (HR: 2.06, 95%CI: 1.36-3.13; *Q*-statistic-*P* = 0.07, I^2 = 51%) regardless of receiving AVT or not (AVT group: HR: 3.14; 95%CI: 1.73-5.69; *Q*-statistic-*P* = 0.60, I^2 = 0%; un-AVT group: HR: 1.73, 95%CI: 1.09-2.76; *Q*-statistic-*P*

= 0.11, I^2 = 50%). The pooled results showed no statistical association between LLV and decompensation of cirrhosis (HR: 2.06, 95%CI: 0.89-4.76; *Q*-statistic-*P* = 0.04, I^2 = 69%), and liver-related events (HR: 1.84, 95%CI: 0.92-3.67; *Q*-statistic-*P* = 0.03, I^2 = 72%), respectively. Grading of Recommendations Assessment, Development and Evaluation assessment indicated moderate certainty for HCC, very low certainty for decompensation of cirrhosis and liver-related clinical events.

CONCLUSION

LLV in compensated cirrhotic patients is associated with increased risk of HCC, higher tendency for hepatic decompensation and liver-related events. Closer screening of HCC should be conducted in this population.

Key Words: Low level of hepatitis B viremia; Compensated cirrhosis; Hepatocellular carcinoma; Hepatic decompensation; Liver-related events

Core Tip: The need for antiviral therapy in patients with compensated cirrhosis and low-level hepatitis B viremia remains debated. This meta-analysis analyzed data from six cohort studies, revealing that low-level viremia in compensated cirrhosis is linked to a higher risk of hepatocellular carcinoma and an increased likelihood of cirrhosis decompensation and liver-related events. These findings support current guidelines for antiviral treatment, underscore the importance of vigilant cancer screening, and highlight the need for regular monitoring of viral levels.

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INTRODUCTION

Chronic hepatitis B is a leading cause of hepatocellular carcinoma (HCC) and the second most common cause of cancer-related mortality. The global prevalence of hepatitis B surface antigen in the general population was 3.8% in 2019, with approximately 1.5 million new hepatitis B virus (HBV) infections, 296 million chronic infections, and 820000 deaths resulting from HBV-related cirrhosis, HCC, or liver failure[1,2]. Given the severity of this situation, the treatment and management of patients with hepatitis B are particularly important. Antiviral therapy (AVT) has improved the prognosis of infected patients through the suppression of viral replication, especially at an early stage of chronic liver disease and even early cirrhosis[3]. However, many patients with compensated cirrhosis with low-level viremia (LLV) remain. Currently, there is no consensus among different guidelines on whether this population should receive AVT. The American Association for the Study of the Liver Diseases and the European Association for the Study of the Liver recommend AVT for these patients[4,5]. Moreover, both China and Japan recommend initiating AVT for cirrhotic patients with detectable HBV DNA[2,6]. In contrast, the Asia-Pacific Association for the Study of the Liver guidelines recommend AVT only for patients with HBV-DNA > 2000 IU/mL[7]. The Korean Association for the Study of the Liver also noted that there is a lack of strong evidence for AVT in this population. To date, no randomized controlled trial (RCT) has evaluated the effect of AVT in patients with LLV and compensated cirrhosis[8]. There is also a subset of the population with LLV even under potent AVT, and whether the risk of HCC in this population is different from that in the population with LLV and without AVT remains unclear. Recent retrospective studies have identified a positive correlation between LLV in compensated cirrhosis and the development of HCC[9,10] while several other studies have reported contradictory findings[11,12]. Currently, there are no prospective studies or meta-analyses that conclusively clarify the relationship between LLV in patients with compensated cirrhosis and HCC.

Considering the inconsistent international guideline recommendations, contradictory observational studies, and the scarce studies on the natural history of patients with compensated cirrhosis and LLV, a systematic review and meta-analysis are needed. We aimed to investigate the association between LLV and HCC risk in compensated cirrhosis patients and to explore whether there is a difference in HCC risk between treated and untreated patients with LLV. Additionally, potential associations between LLV and hepatic decompensation, as well as between LLV and liver-related clinical events, were investigated.

MATERIALS AND METHODS

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis 2009 guidelines. The protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews.

https://www.crd.york.ac.uk/PROSPERO/ - registration number CRD42023405345).

Literature search

Two authors (Lin WC and Lin K) independently searched the PubMed, EMBASE, and Cochrane Library databases for published articles without language restrictions, from inception to March 5, 2023. PubMed is a widely used biomedical database that primarily focuses on studies from the United States. EMBASE complements PubMed by offering broader coverage of European and international journals, particularly in the fields of pharmacology and drug-related research. The Cochrane Library, including the Cochrane Central Register of Controlled Trials, is a key resource for accessing RCTs. The keywords used were as follows: "low-level viremia", "LLV", and "cirrhosis". Additionally, conference abstracts and bibliographies of related literature were screened to identify other articles that might meet the inclusion requirements.

Study selection

The inclusion and exclusion criteria were established according to the PICOS framework (population, intervention, comparison, outcome, and study design). The criteria for considering studies for this review were as follows: (1) Studies that investigated the association of LLV with HCC, hepatic decompensation and liver-related events in patients with compensated cirrhosis; (2) Studies that reported the associated adjusted relative risk (RR)/hazard ratio (HR)/odds ratio (OR) with corresponding 95%CIs or other measures that can be used to compute these values; and (3) Were designed as clinical trials, cohort studies, or case-control studies. The exclusion criteria were as follows: (1) Studies focused on children or adolescents; (2) Certain publication types (animal studies, editorials, letters, and reviews); and (3) Studies with unavailable data. If multiple studies used the same population, the article with the most information or the largest sample size was included. For the definition of outcomes in this study, HCC diagnosis was confirmed by histological evidence or radiological findings determined by dynamic computed tomography and/or magnetic resonance imaging (nodule > 1 cm with arterial hypervascularity and portal/delayed-phase washout)[13]. Decompensated cirrhosis is defined as cirrhosis with severe complications such as ascites, esophagogastric variceal bleeding, or hepatic encephalopathy, with liver function mostly classified as Child-Pugh class B or C[14]. Liver-related events include decompensation of cirrhosis, HCC, liver transplantation, and death[15].

Data extraction and quality assessment

For each article, the study information and basic characteristics were extracted, including the first author, publication year, region, type of study, participants (sample size, sex ratio, age), definition of LLV, baseline ALT (U/L), number of hepatitis B e antigen (HBeAg) positive cases, duration of follow-up, outcomes reported, associated adjusted RR/HR/OR with corresponding 95%CIs, or other measures that could be used to compute these values, and adjustments for confounders. The Newcastle-Ottawa Scale (NOS), a risk of bias assessment tool for observational studies recommended by the Cochrane Collaboration, was used to assess the quality of the included observational studies. Studies with an NOS score > 6 were considered high quality[16]. The overall strength of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, a widely recognized method for evaluating the strength of evidence[17].

Statistical analysis

Aggregate data from the included studies were evaluated *via* meta-analysis, and the random-effects model was applied, considering the potential heterogeneity. The heterogeneity was measured using the Q test ($P < 0.10$ was considered statistically significant) and the I^2 test ($I^2 < 30\%$, = 30%-50%, and > 50% represented low, moderate, and high heterogeneity, respectively)[18]. Funnel plots were used to detect publication bias. For studies where HRs were not provided but Kaplan-Meier curves were available, HRs were calculated according to previous practical guidelines[19]. All statistical analyses were conducted using Review Manager (RevMan) software (version 5.4) (Cochrane Collaboration). A P value for the interaction of less than 0.1 indicated a statistically significant subgroup effect. A two-tailed $P < 0.05$ was considered statistically significant in other analyses.

RESULTS

Study selection

The initial systematic search of the electronic databases identified 363 articles (PubMed: 150; EMBASE: 197; Cochrane Library: 16). After excluding duplicates and screening titles and abstracts, 14 articles underwent a more detailed full-text assessment, of which 8 were further excluded for the following reasons: (1) Not the target population ($n = 3$); (2) Not the target contrast ($n = 1$); or (3) Certain publication types for which data were not available (two were editorials; one was review; one was an abstract, the full article of which has been included in this meta-analysis) (the specific reasons for the excluded studies can be found in Supplementary Table 1). Finally, a total of six studies, including 3155 people, were included in this meta-analysis[9-12,20,21]. The flow chart of the literature search is depicted in Figure 1.

In general, the included studies were retrospective cohort studies with moderate to very low certainty for estimating HCC risk. The pooled results revealed that patients with LLV were associated with an increased risk of HCC regardless of whether they received AVT, but there was no significant association between LLV and decompensation of cirrhosis or liver-related events.

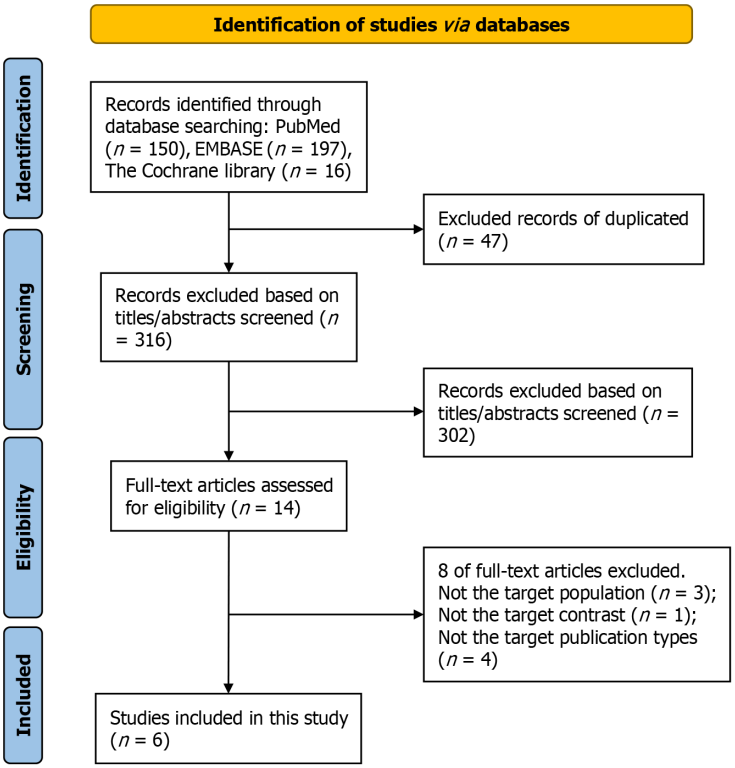

Figure 1 Flowchart of the search and selection process.

Characteristics of the included studies

All six included studies were retrospective cohort studies from Asia, with a total of 3155 patients. Sample sizes ranged from 200 to 1075, with a mean age between 44 and 55.1 years, and follow-up duration ranged from 42 months to 132 months. The prevalence of diabetes varies from 14.8% to 23.7%. With respect to the definition of LLV, three articles defined LLV as HBV-DNA quantification between 20 and 2000 IU/mL[9,11,12], two defined as between 12 and 2000 IU/mL[20,21] and one defined it as between 100 and 2000 IU/mL[10]. All studies reported HCC[9-12,20,21], three reported on hepatic decompensation[10,11,20], and three reported liver-related clinical events[9,10,12]. Additionally, HRs in the two articles were calculated by extracting data from Kaplan-Meier curves, so there were no adjustment factors[10,20] for these studies. Sinn *et al*[21] only provided HRs adjusted for age, whereas the other three studies adjusted for multiple factors, including HBeAg, albumin, and renal function (creatinine or estimated glomerular filtration rate)[9,11,12]. The basic characteristics of the included studies are summarized in Table 1.

Assessment of publication quality

All the observational studies had NOS scores greater than 6, indicating that all the studies were of acceptable quality (Supplementary Table 2 for the specific NOS scoring table). A funnel plot for the associations between outcomes suggested that there was no evidence of publication bias (a funnel plot for the outcomes is shown in Supplementary Figures), although a limited number of included studies is not recommended according to the guidelines. Sensitivity analysis was not conducted due to the small number of articles included in this meta-analysis. The GRADE assessment indicated moderate certainty for the estimates of LLV and increased risk of HCC, very low certainty for the estimates of LLV and decompensation of cirrhosis and liver-related clinical events (the GRADE assessment is shown in Supplementary Table 3).

LLV and the risk of HCC

A total of 6 articles were included to explore the association between LLV and the risk of HCC in patients with compensated cirrhosis (LLV: 1864; undetectable HBV DNA: 1291)[9-12,20,21]. The pooled results revealed that LLV was significantly positively associated with an increased risk of HCC (HR: 2.06, 95%CI: 1.36-3.13; P = 0.0006; Q statistic, P = 0.07; I^2 = 51%), with high heterogeneity (Figure 2A).

Stratified subgroup analysis based on the presence or absence of AVT showed that LLV was significantly associated with an increased risk of HCC regardless of AVT status (AVT: HR: 3.14; 95%CI: 1.73-5.69; P = 0.0002; Q statistic, P = 0.60, I^2 = 0%; un-AVT: HR: 1.73, 95%CI: 1.09-2.76; P = 0.02; Q statistic, P = 0.11, I^2 = 50%). There was no significant difference between the two groups [test for subgroup differences: χ^2 = 2.37, df = 1 (P = 0.12), I^2 = 57.9%; Figure 2B].

LLV and the risk of hepatic decompensation

Three articles were included to investigate the association between LLV and the risk of decompensation of cirrhosis (LLV:

Table 1 Characteristics of included studies

Ref. (first author, year)	Country/region	Type of study	Sample size/LLV/MVR	Age (year)/sex (male%)	Definition of LLV	Baseline ALT (U/L)	HBeAg positive (*n*)	Diabetes (%)	Duration of follow-up	Outcomes reported (HR, 95%CI)	Adjustments for confounders
Huang *et al*[11], 2023	Korea, Singapore, Japan	Retrospective cohort study	1075/742/333	LLV: 55.1/67.8%; MVR: 59.1/72.1%	With ≥ 1 detectable serum HBV-DNA (20-2000 IU/mL)	LLV: 38.5; MVR: 31.2	LLV: 109; MVR: 46	LLV: 16.3; MVR: 19.2	LLV: 62.8 months; MVR: 64.2 months	HCC: MVR Ref LLV 1.20 (0.79, 1.82); Hepatic decompensation: MVR Ref LLV 1.10 (0.66, 1.82)	Sex, diabetes, positive HBeAg, FIB-4 index, Albumin, eGFR, recruitment centers
Lee *et al* [20], 2020	Korea	Retrospective cohort study	440/110/330	LLV: 51.1/80.6%; MVR: 52.9/61.5%	With ≥ 1 detectable serum HBV-DNA (12-2000 IU/mL)	138.3[1]	6.4%[1]	NA	132 months	HCC: MVR Ref LLV 2.64 (1.10, 6.34); Hepatic decompensation: MVR Ref LLV 2.75 (1.39, 5.45)	NA
Lee *et al* [23], 2022	Korea	Retrospective cohort study	567/391/176	54.8/67.9% (LLV: 54.0/66.5%; MVR: 56.7/71.0%)	With ≥ 1 detectable serum HBV-DNA (20-2000 IU/mL)	30.0 (LLV: 30.3; MVR: 29.3)	81 (LLV: 50; MVR: 31)	LLV: 15.1; MVR: 14.8	71.9 months	HCC: MVR Ref LLV 1.42 (0.69, 2.91); Liver-related clinical events: MVR Ref LLV 1.82 (0.84, 3.91)	Age, sex, alcohol consumption, HBeAg, AST, ALT, total bilirubin, albumin, platelet count, and eGFR no. of LLV episodes
Sinn *et al* [21], 2015	Korea	Retrospective cohort study	246/175/71	51.8/66%[1]	With ≥ 1 detectable serum HBV-DNA (12-2000 IU/mL)	24 (median)[1]	11[1]	NA	5.6 years (median)	HCC: MVR Ref LLV 4.79 (1.11, 20.50)	Age
Yang *et al* [9], 2023	Korea	Retrospective cohort study	627/386/241	54.7/64.4% (LLV: 52.2/65.8%; MVR: 58.7/62.2%)	With ≥ 1 detectable serum HBV-DNA (20-2000 IU/mL)	24 (LLV: 25; MVR: 23)	22 (LLV: 19; MVR: 3)	LLV: 16.4; MVR: 23.7	3.9 years	HCC: MVR Ref LLV 2.36 (1.36, 4.11); liver-related clinical events: MVR Ref LLV 1.14 (0.77, 1.70)	Age, AST, ALT, albumin, platelet, total cholesterol, total bilirubin, creatinine, PT, INR, HBeAg, family history, diabetes, hypertension, alcohol drinking, fatty liver
Zhang *et al* [10], 2021	China	Retrospective cohort study	200/60/140	44/72.4%[1]	With ≥ 1 detectable serum HBV-DNA (100-2000 IU/mL)	80[1]	56.7%[1]	NA	42 months	HCC: MVR Ref LLV 3.64 (1.61, 8.20); Hepatic decompensation: MVR Ref LLV 5.11 (1.02, 25.55); Liver-related	NA

		clinical events: MVR Ref LLV 3.59 (1.66, 7.63)

[1]This data is extracted from the total sample of the article.

LLV: Low-level viremia; MVR: Maintained virological response; Ref: reference; HBeAg: Hepatitis B e antigen; HR: Hazard ratio; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; FIB-4 index: Fibrosis 4 Score index; eGFR: Estimated glomerular filtration rate; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; NA: Not available.

912; undetectable HBV DNA: 803)[10,11,20]. The pooled results revealed no significant association between LLV and the risk of decompensation of cirrhosis (HR: 2.06, 95%CI: 0.89-4.76; P = 0.09; Q statistic, P = 0.04; I^2 = 69%), with high heterogeneity (Figure 2C).

LLV and the risk of liver-related clinical events

Three studies investigated liver-related clinical events (LLV: 837; undetectable HBV DNA: 557)[9,10,12]. The pooled results revealed no significant association between LLV and liver-related events (HR: 1.84, 95%CI: 0.92-3.67; P = 0.08; Q statistic, P = 0.03, I^2 = 72%), with high heterogeneity (Figure 2D).

DISCUSSION

In this meta-analysis, we found that patients with LLV and compensated cirrhosis had a significantly greater risk of HCC compared to patients with undetected HBV DNA, regardless of AVT. Additionally, patients in the LLV group had a greater tendency for decompensation and liver-related clinical events.

To the best of our knowledge, this is the first systematic review and meta-analysis to explore the associations between LLV and HCC in patients with compensated cirrhosis. In the absence of RCTs, our results support for the guidelines for AVT in LLV patients. Consistent with our study, several observational studies have emphasized the importance of AVT in LLV patients. A meta-analysis and systematic review published in 2016, which included results of 10 observational studies, found that AVT was associated with a reduced risk of HCC, decompensation, and all-cause mortality in patients with elevated HBV DNA levels of ≥ 4 Log copies/mL and compensated cirrhosis[22]. Furthermore, Lee *et al*[23] recently compared the cost and effectiveness (quality-adjusted life years) of AVT in a virtual cohort of 10000 patients aged 54 years who received AVT *vs* those who did not. Their baseline case analysis simulation found that AVT in LLV patients with compensated cirrhosis contributed positively to clinical benefit and the national health care budget[23].

Regarding the association between LLV after treatment and HCC risk, few relevant studies exist. An observational study from Wong *et al*[24] in 2013 revealed no significant association between AVT and the 3-year risk of hepatitis events, (defined as any cirrhotic complications, HCC, and/or liver-related mortality), when the HBV DNA concentration was less than 2000 IU/L among patients with liver cirrhosis (entecavir cohort: n = 482; control cohort: n = 69; HR 0.80, 95%CI: 0.20-2.10; P = 0.91). However, it is important to note that in this observational study, ALT levels and the HBeAg-positive rate were higher in the control group than in the experimental group, and the sample size of the control group was much smaller than that of the experimental group. The results need to be further validated in future large-scale cohort studies and RCTs.

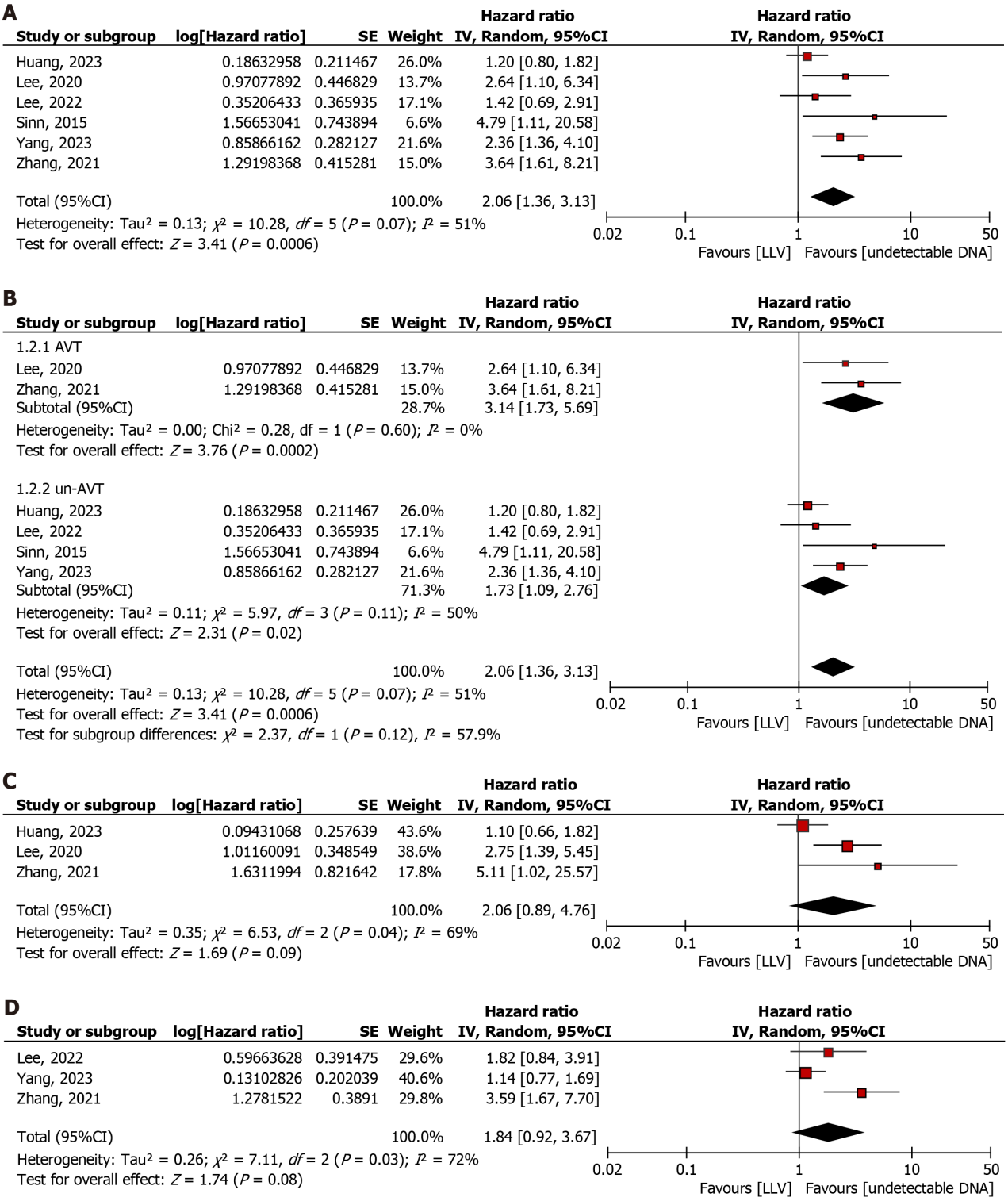

Figure 2 Forest plot. A: Association between low-level viremia (LLV) and hepatocellular carcinoma (HCC); B: Subgroups stratified by the presence or absence of antiviral therapy; C: The association between LLV and hepatic decompensation; D: The association between LLV and liver-related clinical events. The diamond indicates the pooled estimate. Red boxes are relative to the study size, and the black vertical lines indicate the 95%CIs around the effect size estimate.

The mechanisms linking low-level hepatitis B viremia (LLV) to HCC are complex and not fully understood. One key mechanism involves the integration of HBV DNA into the host genome, which may activate proto-oncogenes through insertional mutagenesis. Additionally, HBV proteins interact with host proteins to regulate cell signaling pathways associated with HCC[25,26]. Even at low viremia levels, HBV can induce persistent, low-grade inflammation, leading to sustained immune activation. Over time, this inflammation contributes to liver damage, fibrosis, and cirrhosis, all of which are significant risk factors for HCC[27,28]. Additionally, accumulating evidence from both human and mouse models demonstrates that inflammation facilitates HCC progression by promoting proliferative and survival signaling, inducing angiogenesis, evading immune surveillance, supporting cancer stem cell survival, activating invasion and

metastasis, and inducing genomic instability[29]. Interestingly, LLV is associated with a non-significantly increased risk of liver decompensation and liver-related events. Previous studies have shown that LLV is related to persistent low-grade inflammation, which may affect the dynamic changes in liver fibrosis[30,31]. Whether these changes may increase portal venous pressure, which is known to be highly related to hepatic decompensation events[32] remains unknown. Moreover, a recent Korean study revealed that impaired liver function, rather than LLV, may have a greater impact on liver decompensation[9]. The association between LLV and liver decompensation should be further validated in future investigations.

Given our finding that LLV in patients with compensated cirrhosis is associated with an increased risk of HCC compared with undetectable HBV DNA, regardless of AVT, close monitoring of HBV DNA levels should be emphasized in clinical practice. Recent studies also suggest some solutions for managing patients with LLV. In a prospective study of 211 patients with LLV and chronic hepatitis or compensated cirrhosis, Li *et al*[33] reported that after 12 and 24 weeks of conversion to tenofovir alafenamide fumarate treatment, the virological response rates were 54.7% and 62.7%, significantly higher than those in the control group that continued entecavir treatment (6.7% and 9.3%, respectively)[33]. Furthermore, combination therapy with nucleoside analogs and interferon or pegylated interferon may have better efficacy in achieving a virological response[34].

Our study has several limitations, and the results should be interpreted with caution. First, the included articles were observational studies, which were not sufficient to establish causality. The heterogeneity among studies may compromise the accuracy of the pooled results of our meta-analysis. Second, despite our comprehensive search of databases and related resources, the number of eligible studies remains limited. In addition to studies concerning HCC outcomes, research on hepatic decompensation and liver-related events is sparse. As a result, there are too few studies to conduct a detailed subgroup analysis, and a multifactorial analysis of prognostic factors of LLV is precluded. Prospective studies are needed for further exploration. Third, due to variations in medical practices and measurement equipment across regions, the HBV DNA quantification interval for LLV varied slightly, although every study defined LLV as HBV DNA less than 2000 IU/mL, as the guideline[5]. Fourth, some studies included in the analysis did not adjust for influencing factors, such as HBeAg, which is associated with an increased risk of liver cancer[35]. This lack of adjustment may have introduced errors in the results. Approximately 75% of annual hepatitis B cases are diagnosed in Asia, where the disease is a leading cause of chronic hepatitis, cirrhosis, and HCC[36]. This regional prevalence accounts for the predominance of Asian studies in the literature, but regional variations may effect the generalizability of these findings to other parts of the world.

This meta-analysis highlights the elevated risk of HCC in patients with LLV and compensated cirrhosis compared to those with undetectable HBV DNA, regardless of AVT. Clinicians should prioritize vigilant monitoring of these high-risk patients, employing enhanced surveillance strategies such as more frequent imaging and biomarker testing to enable early detection of HCC. The increased risk of decompensation and liver-related events in the LLV group underscores the need for close management to prevent disease progression. Additionally, further research is needed to elucidate the mechanisms underlying the increased risk of HCC and liver-related events in LLV patients. Future studies should incorporate diverse geographical regions to improve generalizability. Key variables, including baseline HBV DNA levels and HBeAg seropositivity, which are associated with persistent HBV DNA posttreatment and an increased risk of HCC, should be considered. Given that age is a known risk factor for HCC, future studies should also explore the potential differential impact of LLV on prognosis across age groups. Finally, inconsistencies in LLV diagnosis across studies necessitate further investigation to determine whether varying definitions of LLV influence prognosis, ultimately refining hepatitis B surveillance strategies.

CONCLUSION

In summary, LLV in patients with compensated cirrhosis is associated with an elevated risk of HCC. Additionally, patients in the LLV group are more likely to progress to cirrhosis decompensation and other liver-related clinical events. These findings support current guidelines recommending AVT for patients with compensated cirrhosis and LLV. They also highlight the need for vigilant HCC screening in compensated cirrhotic patients with LLV and underscore the importance of monitoring HBV DNA levels in clinical practice. Future prospective studies and randomized trials are essential to further elucidate the relationship between LLV and HCC in patients with compensated cirrhosis.

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FOOTNOTES

Author contributions: Wang X and Wu B conceptualized and designed the study; Lin WC and Lin K developed the search strategy, conducted database research, and drafted the manuscript; Li MK, Liu X, and Huang YF performed data analysis and assisted with result verification; All authors have read and approved the final manuscript. Lin WC and Lin K conducted separate database research,

collaboratively sifted and analyzed the data, and were jointly responsible for drafting the manuscript. Both authors have made significant and indispensable contributions to the project, qualifying them as co-first authors. As co-corresponding authors, Wang X and Wu B conceptualized and designed the study, supervised the research, and revised the manuscript. Wu B applied for and secured funding for the project. He played a crucial role in refining the study design, overseeing the entire project, and providing key revisions to the manuscript. He also ensured the quality and accuracy of the work through final approval of the manuscript. Wang X contributed to data re-analysis and reinterpretation, figure creation, and conducted a comprehensive literature review. The collaboration between Wang X and Wu B has been essential for the completion and publication of this manuscript.

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