Frontiers in **Immunology**

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The load of hepatitis B virus reduces the immune checkpoint inhibitors efficiency in hepatocellular carcinoma patients

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Introduction: Chronic viral infection may lead to an immunosuppressive microenvironment, whereas the association between virus-related indicators and treatment response in hepatocellular carcinoma(HCC) patients undergoing immune checkpoint inhibitors(ICIs) therapy remains a topic of debate. We aim to investigate the influence of hepatitis virus on the ICI efficiency in HCC patients through a meta-analysis.

Methods: We searched PubMed, Cochrane Library, Embase, and Web of Science until 14 July 2024 to identify cohort studies involving ICIs treatments in HCC patients. We extracted data from the literature related to hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, baseline HBV load, and antiviral therapy. Overall survival (OS) and progression-free survival (PFS) were considered as the primary endpoints, while objective response rate (ORR) was regarded as a secondary endpoint.

Results: We included 55 cohort studies published between 2019 and 2024, involving a patient population of 7180 individuals. Summarized hazard ratio (HR) comparing HBV infection with non-HBV infection in the context of ICIs therapy revealed no significant association between HBV infection and either mortality risk or progression risk with the pooled HR for OS of 1.04(95%CI: 0.93-1.16, P=0.483) and the pooled HR for PFS of 1.07(95%CI:0.96-1.20, P=0.342). HBV infected patients with HCC may have better tumor response than non-HBV infected patients receiving ICIs with the combined relative risk(RR) for ORR was 1.94 (95%CI: 1.12-3.38, P=0.002). High baseline HBV load is associated with poor survival outcomes in patients with HCC who receive ICIs with the pooled HR for OS was 1.74 (95%CI: 1.27-2.37, P=0.001), thereby antiviral therapy has the potential to significantly enhance prognostic outcomes with the pooled HR for OS was 0.24 (95% CI: 0.14-0.42 P<0.001) and the pooled HR for PFS was 0.54 (95% CI: 0.33-0.89 P=0.014).

Conclusion: In individuals with HCC who received ICIs, there was no notable link found between HBV or HCV infection and prognosis. However, HBV infection showed a connection with improved tumor response. A higher initial HBV load is linked to worse survival results in HCC patients undergoing ICIs treatment and antiviral therapy can significantly improve its prognosis.

1 Introduction

The latest global cancer statistics report indicates that primary liver cancer continues to be the third leading cause of cancer-related mortality worldwide, with 757,948 individuals succumbing to liver cancer in 2022 (1). Hepatocellular carcinoma (HCC) is the most common type of liver cancer accounting for about 75%-85% of liver cancer (1). Worldwide, the main causes of HCC remain chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection and alcohol abuse, with a predominance of HBV in China, HCV in Japan, non-alcoholic fatty liver disease(NAFLD) and non-alcoholic Steatohepatitis(NASH) and alcohol in Europe and North America (2). The global incidence of HBV-related malignancies has declined since the 2000s because of the implementation of neonatal HBV vaccination programmes (3). Although the prevalence of HBV-driven HCC has declined, the incidence of NAFLD and NASH-related HCC continues to increase because of the increasing prevalence of obesity and the metabolic syndrome, which has hindered the decline of HCC incidence (4).

Due to the lack of typical clinical symptoms in patients with HCC in the early stage, most HCC is diagnosed at an advanced stage and requires systemic treatment. Sorafenib, which was approved as a first-line treatment for HCC in 2007, has improved the survival prognosis of HCC to some extent, but the median overall survival (OS) is only 10.7 months, which is far from clinical expectations (5). The results of the IMbrave150 trial are a milestone in the treatment of HCC, as atezolizumab combined with bevacizumab (median OS: 19.2 months) is significantly better

than sorafenib (median OS: 13.4 months), thus international guidelines endorsed the combination regimen as the new standard of care in front-line treatment of advanced HCC (6). With the reporting of phase III global clinical trials such as CheckMate 459 (7), CARES-310 (8) and COSMIC-312 (9), immune checkpoint inhibitors (ICIs) have further developed in the systemic treatment of HCC, significantly improving the survival prognosis of liver cancer patient. Regrettably, only about 30% of patients with HCC are able to achieve partial response (PR) or complete response (CR) using ICIs therapy, so more markers are needed to screen HCC patients who would respond to ICIs therapy to achieve precise treatment.

HCC is a prototypical inflammation-driven malignancy, and the modulation of immune surveillance within the tumor microenvironment by distinct etiologies may vary, potentially impacting the effectiveness of ICIs. In a cohort of 130 patients with HCC, the presence of NAFLD was found to be significantly associated with reduced median OS following ICIs therapy (5.4 months vs 11.0 months) (10). This may be ascribed to the activation of auto-aggressive CD8+CXCR6+PD1+T lymphocytes by ICIs, which impairs effective immune surveillance and potentially contributes to the development of HCC within the tumor microenvironment (10, 11). In a large cohort study of 1232 patients with HCC, individuals with NASH-related HCC who received treatment with lenvatinib demonstrated significantly improved survival outcomes (22.2 months versus 15.1 months). These results establish a theoretical foundation for categorizing patients with advanced HCC according to the underlying etiology.

In most HCC high-risk areas(China, Eastern Africa,Egypt, Italy, and Japan), HBV infecction and HCV infection is the predominant cause in a diverse set of HCC. Compared with other causes of HCC, the tumor microenvironment of virus-associated HCC has stronger immune inhibition than other causes (1, 12). HBV can lead to PD-1 demethylation and induce functional exhaustion of CD8+ T cells in the tumor microenvironment (TME), thereby facilitating immune evasion by tumor cells (13). HBV can also induce an immunosuppressive microenvironment in the TME by influencing the polarization of tumor-associated macrophages (TAM), as well as modulating levels of IL-6 and IL-8 (14–16). Due to the intricate nature of theTME in HBV-HCC, the association between this environment

and the efficacy of ICIs therapy remains a subject of intense debate. A meta-analysis of three large randomized controlled phase III clinical trials (CheckMate-459 (7), IMbrave150 (6), and KEYNOTE-240 (17)) which evaluate the clinical benefit by comparing the ICI treatment with non-ICIs therapy treatments (including placebo and sorafenib) in advanced HCC patients, found that the difference of treatment efficiency (OS) was more remarkable for the ICI vs non-ICI analysis in HBV-HCC patients when compared with those of ICI vs non-ICI analysis in non-HBV-HCC patients, while none performed the direct comparison for the stratified analysis of ICI treatment efficiency between HBV-HCC and non-HBV-HCC patients. In this article, we conduct a meta-analysis to explore the association between HBV infection and the outcomes of HCC patients undergoing ICIs therapy.

A high baseline HBV load is associated with poor prognosis in patients treated with sorafenib, as well as being an independent risk factor for low survival rates and early recurrence after curative resection in HCC patients (18–20). There is ongoing debate regarding the association between baseline HBV load and prognosis in patients with HCC undergoing treatment with ICIs. Several retrospective studies with small sample sizes have indicated that baseline viral load does not exhibit a significant correlation with OS (21), and these findings are constrained by limited sample size. We conducted a meta-analysis to further investigate the correlation between HBV load and the prognosis as well as tumor response in HCC patients treated with ICI. Previous research has indicated that antiviral therapy for HBV can significantly enhance the survival outcomes of ICIs patients undergoing antiangiogenic therapy or ICIs therapy (18, 21). Our study aims to conduct a meta-analysis to verify the impact of both HBV load and antiviral therapy on treatment efficiency of ICI in HCC patients.

2 Materials and methods

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

2.1 Literature search strategy

We systematically searched multiple electronic databases, covering PubMed, Embase,Cochrane and Web of science for all the available articles published before 14 July 2024. The search terms mainly included the following words: "Immune checkpoint inhibitors", "Pembrolizumab", "Nivolumab", "Atezolizumab", "Durvalumab","Tislelizumab", "Camrelizumab", "Sintilimab", "Carcinoma, Hepatocellular", "Survival Rate", "Prognosis". It should be noted that only publications in English were considered for inclusion.

2.2 Study selection

Inclusion criteria:(1) Study design type: cohort studies about the treatment of HCC with ICIs. (2) Study object: patients diagnosed with HCC, as confirmed by imaging evidence or pathological evidence; (3) Intervention measures: ICIs monotherapy or ICIs combined with targeted drug.

Exclusion criteria: (1) Duplicated articles; (2) Articles that were reviews, Bioinformation analyses, meeting summaries, case reports, animal experiments, expert consensuses, or editorials; (3) Articles that did not specify the type of research; (4) Articles that did not provide outcomes needed; (5) Studies with too small a sample size (sample size < 40); (6) Articles in other languages than English.

2.3 Data extraction

Screening and data extraction processes were conducted by two independent reviewers, and the differences were resolved by a third reviewer. For each included study, the following information was extracted: name of the study, publication year, the first author, study type, geographical region, number of patients, demographics and baseline characteristics of included patients, line of therapy, treatment strategy, clinical stage, follow-up time.

2.4 Quality assessment.

The quality of the cohort studies was evaluated with the Newcastle Ottawa scale (NOS). There were 9 stars in the article quality evaluation, and articles with 6 stars or more were retained.

2.5 Statistical analysis

Stata 15.1 analysis software was used to statistically analyze the relevant outcome indicators. The summary measure was the hazard ratios (HRs) and 95% confidence interval (95%CI) for OS and progression-free survival (PFS), $P < 0.05$ was considered statistically significant. The Cochrane Q statistic (significant at $P < 0.10$) and I^2 value (significant heterogeneity if >50%) were used to evaluate heterogeneity. If $I^2 < 50\%$ or $P > 0.10$, then the heterogeneity was considered to below and fixed-effects model was applied. Otherwise, the random-effects model was applied. The sensitivity analysis was carried out by RevMan 5.3, and the risk of publication bias was determined using Begg's tests and Egger's. When $P > 0.05$, there was considered to be no publication bias. If the number of included articles was less than 10, no further bias test was required.

3 Results

3.1 Selection process

The two reviewers independently devised search strategies. After an initial examination, a total of 6684 pertinent studies were identified, comprising 6649 records from the database search and an additional 35 records from manual searching. Among these, 1083 articles were deemed potentially relevant following title and abstract screening. Subsequent screening led to the selection of 168

articles for further evaluation. Following a thorough assessment of the remaining 168 studies' full texts, we included 55 cohort studies published between 2019 and 2024, encompassing a patient population of 7180 individuals. Figure 1 presents a flow chart illustrating the process employed for study selection.

3.2 Quality evaluation

NOS was used to evaluate the quality of the 55 cohort studies, and they were found to have a NOS score≥6, indicating medium-to-high quality(Supplementary Table S1).

3.3 Study and patient characteristics

A total of 54 enrolled articles, published between 2019 and 2024, included 54 cohort studies. Of the 54 cohort studies, 37 were from China, 5 from Taiwan China, 5 from Global, 3 form France, 1 form Korea, 1 form Austria, 1 form Thailand, 1 form USA, 1 from Singapore. In 7 studies, all patients received ICIs monotherapy; in 19 studies, patients were treated with immunotherapy combined with antiangiogenic therapy; in the other 29 studies, patients were partially treated with ICIs monotherapy and partially treated with combined immunotherapy (combined with antiangiogenic therapy or locoregional therapy). The features of the chosen studies can be observed in Table 1.

3.4 Evaluation of survival outcomes

In the 35 cohort studies that provided HRs of HBV infection vs Non-HBV infection for OS (22–56), the combined HR for OS was 1.04(95%CI: 0.93-1.16, P=0.483 Figure 2A), indicating low heterogeneity (I^2 = 0.0%, P=0.704), suggested that HBV infection was not associated with the risk of death in HCC patients treated with ICIs. Of the 35 cohort studies, 17 studies of 2021 HCC patients investigated the combination of ICIs with targeted therapy, whereas 3 studies evaluated ICIs monotherapy including 395 HCC patients. For the OS of HBV infection vs Non-HBV infection, subgroup analysis showed that the pooled HR of the combination of ICIs with targeted therapy group was 1.14 (95%CI: 0.96-1.35, P= 0.131, Supplementary Figure S1A) and that of the ICIs monotherapy group was 1.19 (95% CI:0.77-1.86, P= 0.434, Supplementary Figure S1B) with no significant difference between the two groups (P= 0.849).

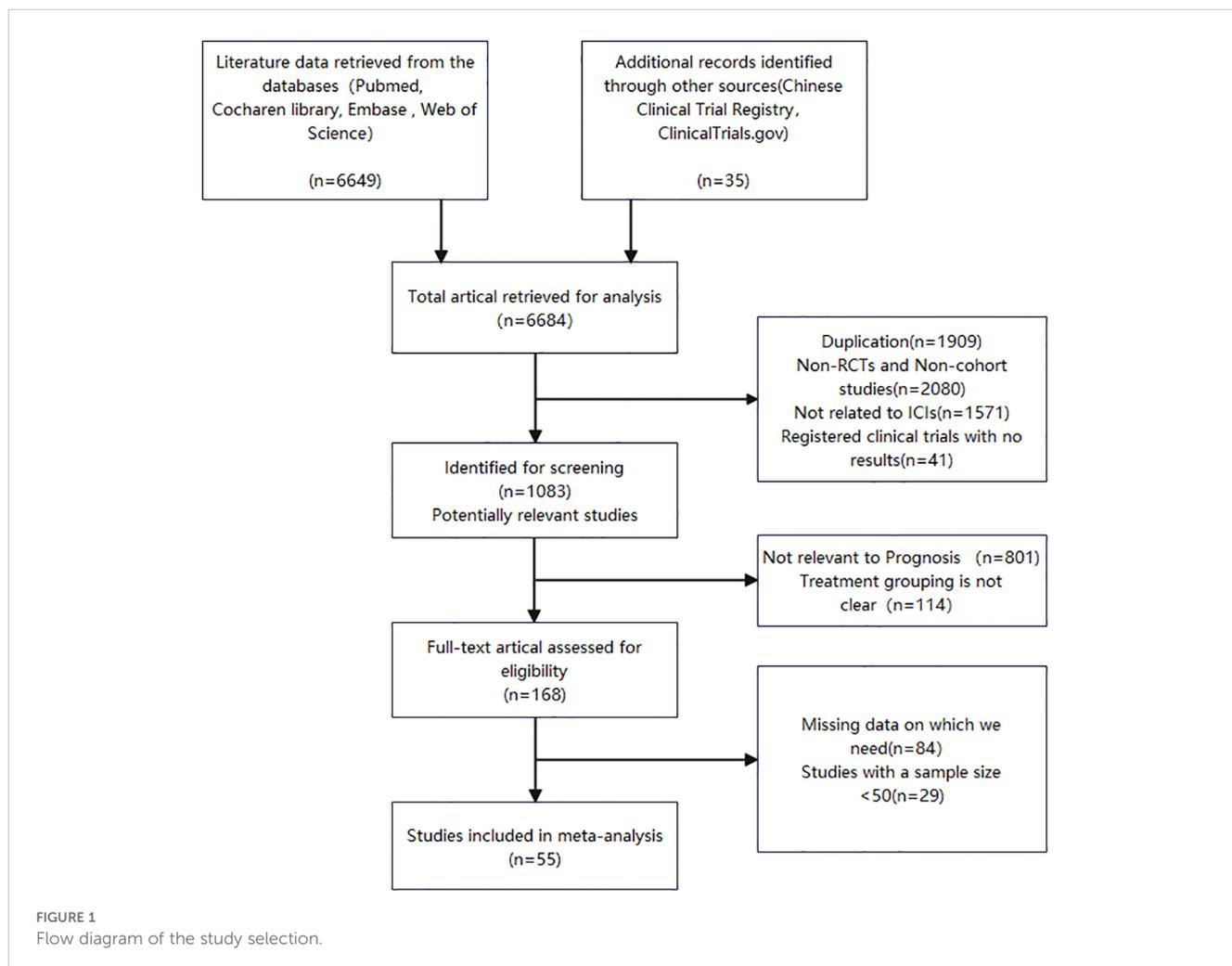**FIGURE 1**
Flow diagram of the study selection.

TABLE 1 Characteristics of the 55 cohort studies incorporated in the meta-analysis.

Study	Published	Geographical Area	Research Type	Treatment Strategy	No. of Patients total
Kennedy Yao Yi Ng et al.	2020	Singapore	RCS	ICI monotherapy/Combination ICI therapy	114
Guosheng Yuan et al.	2021	China	RCS	Combination ICI therapy	86
Haonan Liu et al.	2022	China	RCS	ICI monotherapy	54
Mengchao An et al.	2022	China	RCS	ICI monotherapy/Combination ICI therapy	217
Xuqi Sun et al.	2020	China	RCS	ICI monotherapy/Combination ICI therapy	253
Guosheng Yuan, et al.	2020	China	RCS	Combination ICI therapy	63
Rohini Sharma et al.	2021	Global	PCS	ICI monotherapy/Combination ICI therapy	420
Yanjun Shen et al.	2021	China	RCS	Combination ICI therapy	57
Shuguang Ju et al.	2022	China	RCS	Combination ICI therapy	108
Pei-Chang Lee et al.	2020	Taiwan, China	RCS	ICI monotherapy/Combination ICI therapy	90
Petros Fessas et al.	2020	Global	RCS	ICI monotherapy	233
Song Chen et al.	2021	China	RCS	Combination ICI therapy	170
Junlin Yao et al.	2021	China	RCS	Combination ICI therapy	136
Fucun Xie et al.	2022	China	RCS	Combination ICI therapy	85
Francisca-Dora Copil et al.	2023	France	RCS	Combination ICI therapy	295
Jaekyung Cheon et al.	2023	Korea	RCS	Combination ICI therapy	169
Yujing Xin et al.	2023	China	RCS	Combination ICI therapy	118
Lorenz Balcar et al.	2023	Austria	RCS	ICI monotherapy/Combination ICI therapy	72
Jing Li et al.	2023	China	RCS	Combination ICI therapy	110
Huttakan Navadurong et al.	2023	Thailand	RCS	Combination ICI therapy	83
Mathew Vithayathil et al.	2022	Global	RCS	Combination ICI therapy	191
Claudia Campani et al.	2022	France	RCS	Combination ICI therapy	75
Yue Linda Wu et al.	2022	Global	RCS	Combination ICI therapy	296
Dongbo CHEN et al.	2023	China	RCS	Combination ICI therapy	86
De-Zhen Guo et al.	2023	China	RCS	Combination ICI therapy	129
Xindan Kang et al.	2023	China	RCS	ICI monotherapy/Combination ICI therapy	85
Qingyan Liu et al.	2023	China	RCS	ICI monotherapy/Combination ICI therapy	94
Xinhua Zou et al.	2023	China	RCS	Combination ICI therapy	80
Xu Chang et al.	2023	China	RCS	Combination ICI therapy	97
Zhongjing Huang et al.	2024	China	RCS	Combination ICI therapy	123
Fei Cao et al.	2023	China	RCS	Combination ICI therapy	139
Huilan Zeng et al.	2023	China	RCS	Combination ICI therapy	152

(Continued)

TABLE 1   Continued

Study	Published	Geographical Area	Research Type	Treatment Strategy	No. of Patients total
Kang Wang et al.	2023	China	RCS	Combination ICI therapy	159
Xiaoyun Hu et al.	2022	China	RCS	Combination ICI therapy	70
Lu-shan Xiao et al.	2022	China	RCS	ICI monotherapy/Combination ICI therapy	172
Jia-Ren Wang et al.	2022	China	RCS	ICI monotherapy/Combination ICI therapy	215
Yusheng Guo et al.	2022	China	RCS	ICI monotherapy/Combination ICI therapy	97
Bang-Bin Chen et al.	2022	Taiwan, China	RCS	ICI monotherapy/Combination ICI therapy	138
Haonan Liu et al.	2022	China	RCS	ICI monotherapy	54
Bai-Bei Li et al.	2024	China	RCS	ICI monotherapy	160
Lei Xu et al.	2023	China	RCS	ICI monotherapy	85
Baizhu Xiong et al.	2023	China	RCS	ICI monotherapy	74
Jiajia Du et al.	2024	China	RCS	ICI monotherapy/Combination ICI therapy	124
Wei-Fan Hsu et al.	2023	Taiwan, China	RCS	ICI monotherapy/Combination ICI therapy	110
Lu-Shan Xiao et al.	2022	China	RCS	ICI monotherapy	161
Yue Chen et al.	2024	China	RCS	Combination ICI therapy	56
Philippe Sultanik et al.	2024	France	PCS	Combination ICI therapy	200
Jiaxin Han et al.	2024	China	RCS	ICI monotherapy/Combination ICI therapy	155
Di Pan et al.	2024	China	RCS	Combination ICI therapy	110
Darren Cowzer et al.	2024	United States	RCS	ICI monotherapy/Combination ICI therapy	91
Jiao Zhang et al.	2024	China	RCS	ICI monotherapy/Combination ICI therapy	80
Kun-Peng Ma, et al.	2024	China	RCS	Combination ICI therapy	102
Bang-Bin Chen et al.	2024	Taiwan, China	RCS	ICI monotherapy/Combination ICI therapy	143
Wen-Chi Wu et al.	2022	Taiwan, China	RCS	Combination ICI therapy	40
Michael S Lee et al.	2020	Global	PCS	ICI monotherapy/Combination ICI therapy	104

PCS, prospective cohort study; RCS, retrospective cohort study.

In the 25 cohort studies that provided HRs of HBV infection vs Non-HBV infection for PFS (25–29, 35, 36, 38, 40, 57, 58), the combined HR for PFS was 1.07(95%CI:0.96-1.20, P=0.342 Figure 2B), indicating low heterogeneity (I^2 = 32.2%, P=0.063), suggested that HBV infection was not associated with the risk of progression in HCC patients treated with ICIs. Of the 25 cohort studies, 13 studies of 1575 HCC patients investigated the combination of ICIs with targeted therapy and 4 studies evaluated ICIs monotherapy with 449 HCC patients. For the PFS of HBV infection vs Non-HBV infection, subgroup analysis showed that the pooled HR of the combination of ICIs with targeted therapy group was 1.12 (95%CI: 0.93-1.36, P= 0.292, Supplementary Figure S1C) and that of the ICIs monotherapy group was 1.1 (95% CI: 0.89-1.59, P= 0.241, Supplementary Figure S1D) with no significant difference between the two groups(P= 0.943).

In the 3 cohort studies that provided objective response rate (ORR) of HBV infection vs Non-HBV infection with 177 HCC patients (59–61), the combined relative risk(RR) for ORR was 1.94 (95%CI: 1.12-3.38, P=0.002 Figure 2C), indicating low heterogeneity (I^2 = 0.0%, P=0.561), suggested that HBV infected patients with HCC may have better response than non-HBV infected patients receiving ICIs.
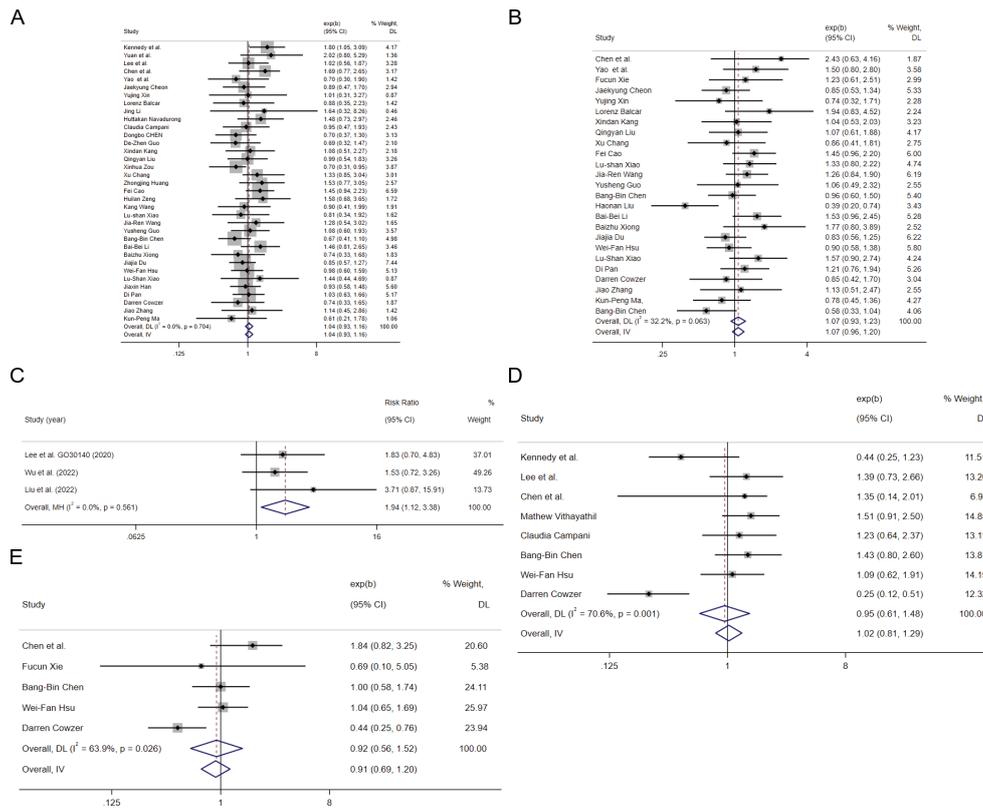
FIGURE 2

The tree diagram for HBV infection group and HCV infection group. Squares indicated study-specific effect size. Horizontal lines represent the 95% CIs. Diamonds represent the pooled effect size. The dashed vertical lines indicate the pooled effect size for immune checkpoint inhibitors. The P value for heterogeneity is obtained from the meta-analysis of the interaction. **(A)** pooled HR of OS on HBV infection vs. Non-HBV infecction; **(B)** pooled HR of PFS on HBV infection vs. Non-HBV infecction; **(C)** pooled RR of ORR for HBV infection vs. Non-HBV infecction; **(D)** pooled HR of OS on HCV infection vs. Non-HCV infecction; **(E)** pooled HR of PFS on HCV infection vs. Non-HCV infecction.

In the 7 cohort studies that provided HRs of HCV infection vs Non-HCV infection for OS (22, 24, 25, 32, 46, 50, 62), the combined HR for OS was 1.20(95%CI:0.94-1.53, P=0.236 Figure 2D), indicating low heterogeneity (I^2 = 20.9%, P=0.270), suggested that HBV infection was not associated with the risk of death in HCC patients treated with ICIs. In the 4 cohort studies that provided HRs of HCV infection vs Non-HCV infection for PFS (25, 46, 50, 57), the combined HR for PFS was 1.15(95%CI:0.84-1.57, P=0.393 Figure 2E), indicating low heterogeneity (I^2 = 0.0%, P=0.484), suggested that HCV infection was not associated with the risk of progression in HCC patients treated with ICIs.

In the 3 cohort studies that provided HRs of high HBV-DNA replication vs low HBV-DNA replication for OS (41, 53, 63), the combined HR for OS was 1.74(95%CI: 1.27-2.37, P=0.001 Figure 3A), indicating low heterogeneity (I^2 = 1.7%, P=0.362), suggested that high HBV-DNA replication is associated with a higher risk of death in HCC patients treated with ICIs. In the 4 cohort studies that provided HRs of high HBV-DNA replication vs low HBV-DNA replication for PFS (52, 53, 63, 64), the combined HR for PFS was 1.25 (95%CI: 0.98-1.60, P=0.07 Figure 3B), indicating low heterogeneity (I^2 = 0.0%, P=0.702), suggest that higher HBV-DNA replication levels tend to be associated with a

higher risk of progression in HCC receiving ICIs. Three cohort studies that provided high HBV-DNA versus low HBV-DNA efficacy indicators were pooled, with an RR for ORR (53, 64, 65) of 0.75 (95%CI: 0.50-1.13, P=0.169 Figure 3C), and an RR for disease control rate (DCR) (53, 64, 65) of 0.95 (95%CI: 0.81-1.11, P=0.528 Figure 3D), suggesting that the level of HBV-DNA replication is not significantly related to treatment renponse of ICIs in patients with HCC.

Summarizing 2 articles containing data on the HR for OS and PFS in relation to receiving anti-HBV treatment versus not receiving anti-HBV treatment (53, 63), the results indicate that the HR for overall survival OS is 0.24 (95%CI: 0.14-0.42 P<0.001 Figure 3E), and the HR for PFS is 0.54 (95%CI: 0.33-0.89 P=0.014 Figure 3F). These findings suggest that administering antiviral treatment during ICIs therapy can significantly ameliorate the prognosis of patients with HCC.

Fourteen cohort studies of 2277 patients with 514 cases of alcohol-related HCC was used to evaluate the association for alcohol etiology with survival (22, 26, 31, 32, 43, 44, 50, 51, 53, 57, 66–69). The pooled HR for OS is 1.00 (95%CI: 0.84-1.20, P= 0.855 Supplementary Figure S2A), and the HR for PFS is 1.05 (95% CI: 0.87-1.28, P= 0.589 Supplementary Figure S2B). These findings

indicated that alcohol etiology is not significantly associated with the prognosis of HCC patients with ICIs treatment.

There are 5 cohort studies of 772 HCC patients with 224 cases of NASH-related HCC was used to evauate the association for NASH with survival (22, 29, 31, 32, 68). The pooled HR for OS is 1.19 (95%CI: 0.92- 1.52, P= 0.181 Supplementary Figure S2C), suggested NASH is not significantly associated with the OS of HCC patients receiving ICIs. Only one study focus on the PFS of NASH-HCC, which made the PFS analysis uneffectively be carried out.
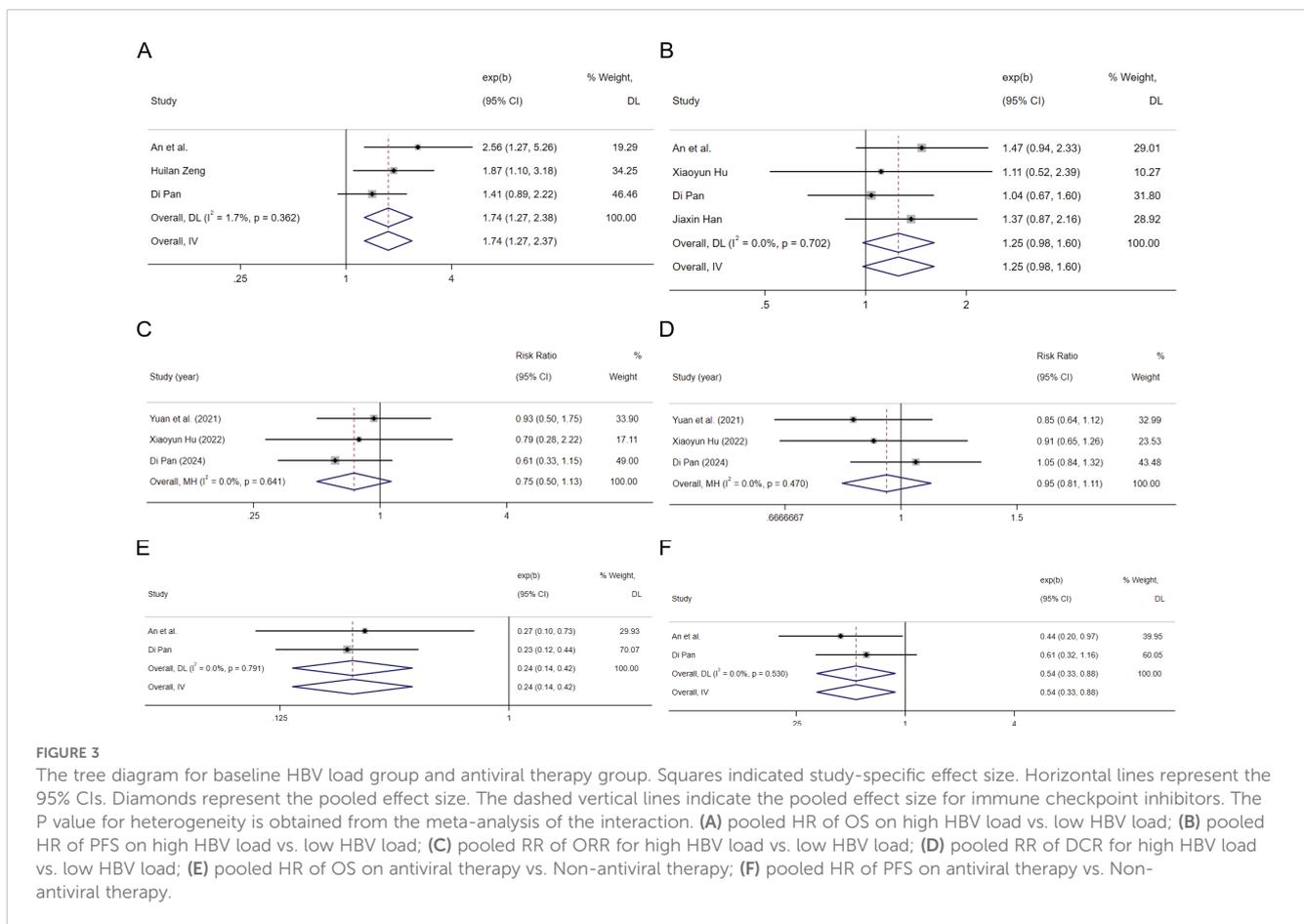
There are 28 cohort studies that provide HR for cirrhosis (21, 25, 26, 58, 63, 66, 70–73). The pooled HR for OS is 1.16 (95%CI: 1.04-1.31, P=0.011 Supplementary Figure S2D), and the HR for PFS is 1.06 (95%CI: 0.96-1.18, P=0.252 Supplementary Figure S2E). These findings suggest an increased risk of mortality in patients with cirrhosis for HCC patients receiving ICIs.

3.5 Sensitivity analysis and publication bias

To evaluate the robustness and reliability of the calculated results, a sensitivity analysis was performed(Supplementary Figure S3). The findings suggest that excluding any literature in this study has no impact on the obtained results (Figure 4, Supplementary Figure S4). Based on the outcomes of Begg's tests and Egger's tests, there is no indication of publication bias in this study (Supplementary Table S2).

4 Discussion

ICIs enhances the anti-tumor activity of the immune system by inhibiting immune downregulating factors such as programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4) (74). ICIs exert their effects on the immune microenvironment surrounding tumors, and it has been demonstrated that CD8+ T lymphocytes, B cells, IL-6, and tertiary lymphoid structures (TLS) within tumor tissue all play a role in influencing the prognosis of ICI therapy for tumors (75–77). It has been reported that factors such as gut microbiota, antibiotic application, growth hormone, systemic inflammation response index and sarcopenia can predict the prognosis of malignant tumor patients treated with ICIs (78–84). Heterogeneity in the tumor microenvironment, influenced by various etiologies of HCC, may impact the efficacy of ICIs. Nevertheless, the association between the etiology of HCC and the prognosis as well as tumor response in patients treated with ICIs remains poorly understood. In a retrospective cohort study of 429 patients undergoing ICIs for HCC, Brown et al. observed that the three common causes of NASH, alcohol consumption, and viral infection did not exhibit a significant association with patient OS (68). Our study provides a comprehensive evaluation of the correlation between virus-related indicators and the outcomes of ICIs in patients with HCC, expanding upon the groundwork laid by our predecessors.

FIGURE 3

The tree diagram for baseline HBV load group and antiviral therapy group. Squares indicated study-specific effect size. Horizontal lines represent the 95% CIs. Diamonds represent the pooled effect size. The dashed vertical lines indicate the pooled effect size for immune checkpoint inhibitors. The P value for heterogeneity is obtained from the meta-analysis of the interaction. **(A)** pooled HR of OS on high HBV load vs. low HBV load; **(B)** pooled HR of PFS on high HBV load vs. low HBV load; **(C)** pooled RR of ORR for high HBV load vs. low HBV load; **(D)** pooled RR of DCR for high HBV load vs. low HBV load; **(E)** pooled HR of OS on antiviral therapy vs. Non-antiviral therapy; **(F)** pooled HR of PFS on antiviral therapy vs. Non-antiviral therapy.
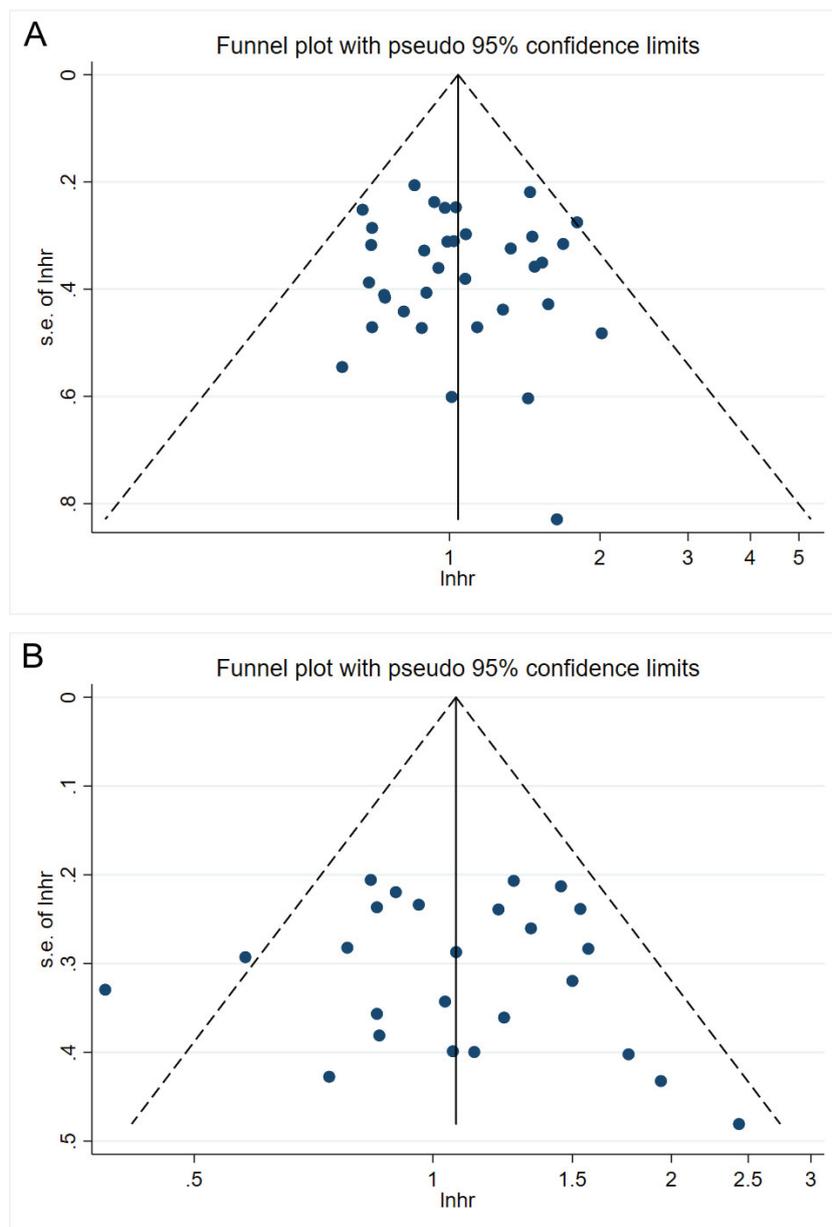
FIGURE 4
Funnel plots. **(A)** 35 cohort studies that provided HRs for OS on HBV infection vs. Non-HBV infecction. **(B)** 25 cohort studies that provided HRs for PFS on HBV infection vs. Non-HBV infecction.

Our study revealed that neither HBV infection nor HCV infection exhibited a significant association with the risk of mortality or disease progression in HCC patients undergoing treatment with ICIs, and subgroup analysis also showed the HBV infection was associated with neither PFS nor OS in each subgroup (ICI monotherapy or ICI combination therapy). However, HBV infection displayed superior tumor response of HCC patients treated with ICIs compared to non-HBV infection. In a fundamental clinical trial conducted by Hsu et al, it was observed that the expression of PD-1 on tumor-infiltrating lymphocytes exhibited a statistically significant increase in patients with HBV-HCC (85). Gao et al. observed a relatively high mutation frequency of AXIN1, TSC2, ATRX, and KMT2C genes in the HBV infection

cohort, which are associated with enhanced efficacy of ICIs (86). Both of these findings suggest that HBV-related HCC may benefit from ICIs therapy, however, our study only found an advantage in tumor response, without finding a significant survival benefit for HBV-infected patients receiving ICIs compared to non-HBV-infected patients. Ping-Ning Hsu et al. also found that the expression of PD-1 on tumor-infiltrating lymphocytes was lower in patients with portal vein tumor thrombosis(PVTT) compared to those without PVTT (85). In patients diagnosed with HCC, PVTT is present in 10-40% of cases (87). This provides us with a research direction for further in-depth exploration: investigating the association between PVTT or different metastasis sites in HBV-HCC patients and the outcomes following the application of ICIs.

The study involving 45 HBV-related HCC patients indicate that patients with HBV-HCC harboring the HBV Pre-S2 Mutant exhibit elevated PD-L1 expression compared to other HBV-HCC patients. This observation prompts further investigation into the differential response to ICIs in HCC patients with distinct HBV mutation sites.

The viral load of other virus-associated malignancies has also been documented to impact the clinical outcomes of ICIs, including gastric cancer and anal cancer (88, 89). For HBV-HCC, multiple retrospective studies have indicated that there is no significant association between HBV load and the prognosis of ICIs therapy (19). Our meta-analysis revealed a different result, demonstrating that high HBV DNA load was correlated with an elevated risk of mortality in HCC patients undergoing ICIs treatment. In comparison with other studies, our study stands out due to its larger sample size with 6 studies and 704 patients. Firstly, HBV promotes hepatic fibrosis by integrating genes into liver cells, regulating microRNAs, promoting oxidative stress, and activating carcinogenic signaling pathways to facilitate the development of HCC. In the presence of a high HBV viral load, immune checkpoint inhibitors are unable to fully counteract the carcinogenic effects of HBV (90–93). Secondly, high HBV load itself increases the aggressiveness and metastatic potential of HCC, thus interfering with the anti-tumor effects of ICIs (93). Thirdly, a high HBV load may also lead to the upregulation of IL-6 levels through the NF-κB pathway, and elevated IL-6 has been linked to unfavorable prognosis in patients undergoing ICIs treatment (94). The aforementioned mechanisms partially account for the heightened mortality risk observed in HCC patients with elevated HBV load undergoing treatment with ICIs.

In previous studies, antiviral therapy has demonstrated efficacy in the prevention of HCC in patients with chronic hepatitis B, as well as in reducing the recurrence of HBV-related HCC and improving postoperative survival rates (95). Consistent with the retrospective study by An et al. (63), our pooled data suggest that antiviral therapy can significantly improve survival outcomes in HCC patients receiving ICIs. Effective antiviral therapy can effectively inhibit HBV replication, decrease serum viral load, expedite the seroconversion of hepatitis Be antigen (HBeAg), thereby partially alleviating or delaying liver function deterioration and enhancing survival rate (96). Antiviral therapy can also alter T cell function, with CD8+ tumor-infiltrating lymphocytes expressing higher effector T cell markers and lower T cell exhaustion markers in patients receiving antiviral therapy, playing a adjuvant role in the anti-tumor effects of ICIs (63).

Our findings have significant clinical implications, and monitoring viral load throughout HBV-HCC treatment is imperative. Timely adjustment of effective antiviral medications upon detection of viral replication can substantially impact the prognosis of patients. While antiviral therapy may enhance the clinical prognosis of HCC patients, the survival outcomes for advanced HCC patients treated with ICIs remain suboptimal. It is still necessary for researchers to actively explore predictive factors of ICIs, create prediction models, so as to precisely select the beneficiaries of immune checkpoint inhibitors and achieve individualized treatment.

The previous report including 130 HCC patients with 13 cases of NASH-related HCC demonstrated that NASH was associated with a poorer prognosis for the HCC patients with ICIs treatment (10). But the association for NASH with the poorer prognosis of ICI treatment was not found in our analysis which including 772 HCC patients with 224 cases of NASH-related HCC. The accuracy of the final results may be affected by the research subjects from different regions and ethnicities, the different etiologies of HCC included in control groups, the different ICI antibodies and the different follow-up periods.

There are some limitations to this study. Firstly, some of the included studies were retrospective cohort studies with limitations and inevitable selection bias. Secondly, although the review was not officially recorded, we conducted the meta-analysis adhering strictly to the guidelines outlined in the PRISMA statement. Furthermore, the fact that this meta-analysis did not explore the impact for HBV mutation sites, portal vein thrombosis, or different metastasis sites on the prognosis of HBV-HCC patients with ICIs treatment might affect the accuracy of the analysis. Although we previously identified outcome associated mutations for postoperative HCC patients and furtherly performed the functional analysis for their contribution on HCC growth, the ICI treatment efficiency analysis requires a large number of patients as the frequency for each candidate mutation does not exceed 20% (97, 98). Further subgroup analyses should be conducted according to HBV mutation sites, portal vein thrombus, etc. to further assess the relationship between these factors and the prognosis of HBV-HCC patients treated with ICIs.

5 Conclusion

In patients with HCC treated with ICIs, there was no significant correlation between HBV or HCV infection with prognosis, while HBV infection was associated with better tumor response. Higher baseline HBV load is associated with poorer survival outcomes in patients with HCC who receive ICIs therapy, and antiviral therapy can significantly improve the prognosis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

Author contributions

ZJ: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. JL: Writing – original draft. SZ: Writing – original draft. YJ: Writing – original draft. JZ: Conceptualization, Supervision, Writing – review & editing. ZG: Conceptualization, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1480520/full#supplementary-material

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