Hindawi
Journal of Oncology
Volume 2023, Article ID 2525903, 13 pages
https://doi.org/10.1155/2023/2525903

Review Article

Efficacy and Safety of Immune Checkpoint Inhibitors in Patients with Cancer and Hepatitis B or C: A Systematic Review and Meta-Analysis

Huijing Dong,[1] **Chongxiang Xue**,[1] **Yumin Zheng**,[1] **Xu Zhang**,[1] **Zixin Hu**,[1] **Xingyu Lu**,[1] **Yixuan Yu**,[1] **Jia Li**,[1] **Kexin Tan**,[1] **and Huijuan Cui**[2]

[1]*Beijing University of Chinese Medicine, Beijing, China*
[2]*Department of Integrative Oncology, China-Japan Friendship Hospital, Beijing, China*

Correspondence should be addressed to Huijuan Cui; cuihj1963@sina.com

Received 30 November 2022; Revised 12 December 2022; Accepted 14 December 2022; Published 7 January 2023

Academic Editor: Alessandro Granito

Copyright © 2023 Huijing Dong et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Immune checkpoint inhibitors (ICIs) have changed the situation of tumor therapy in recent years. However, for security reasons, those special populations are often excluded from clinical trials, such as infected hepatitis B or hepatitis C patients. ICIs are systematically reviewed and meta-analyzed for the first time in patients infected with hepatitis B or C in this paper. *Methods*. The relevant studies were searched in PubMed, EMBASE, Cochrane Library, and Web of Science until October 2022. Trials and observational studies meeting the inclusion criteria were included. The outcomes included the effectiveness of ICIs in patients with HBC/HCV (ORR, DCR, mOS, and mPFS), the incidence of adverse reactions, high-grade adverse reactions, and abnormal liver enzymes. At the same time, these indexes were compared with those of uninfected patients. *Results*. A total of 2,625 patients were enrolled, involving 1,179 patients with hepatitis (HBV or HCV). We found that ICIs showed higher ORR (25.80% vs. 18.10%) and DCR (66.22% vs. 58.74%) in patients with hepatitis B/C than those without infection. In terms of survival time, patients with hepatitis virus infection showed longer mOS (15.44 m vs. 13.30 m) but shorter mPFS (4.94 m vs. 5.01 m) than uninfected patients. As for safety data, patients with hepatitis showed a lower incidence of all-grade irAEs (68.02% vs. 70.43%) than uninfected patients, while that of 3-4 irAEs (21.27% vs. 21.79%) was similar in the two groups. However, hepatic dysfunction was more common and serious in hepatitis patients. Four HBVr and no HCVr were observed. *Conclusion*. According to this meta-analysis, ICIs are effective and safe for patients with hepatitis B or C, but basic liver enzymes have to be evaluated before treatment to avoid liver adverse events.

1. Introduction

Over the past few years, the immune checkpoint inhibitors (ICIs) that target programmed cell death receptor-1 (PD-1), programmed cell death-ligand 1 (PDL1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have shown encouraging efficacy in a variety of tumor types such as lung cancer, melanoma, and liver cancer [1]. Although ICIs have presented a revolutionary alternative therapeutic approach for patients with tumor, its adverse reactions also pose a threat to them.

Hepatitis C virus (HCV) and hepatitis B virus (HBV) are the main causes of chronic liver disease worldwide and are the leading causes of liver cancer and overall mortality globally [2, 3]. The total infection prevalence of HBV worldwide has risen to 3.9%, which means that at least 292 million people suffer from HBV [3]. As for HCV, about 71 million people worldwide are chronically infected with the hepatitis C virus [2]. Regardless of the fact that there are not a small number of people with hepatitis, these patients are often excluded from ICIs clinical trials for the associated theoretical risk of hyperimmune response or causing

hepatitis B/C reactivation. Taking into account this concern, there is limited evidence of the safety and efficacy of ICIs in patients with viral hepatitis.

The Checkmate 040 study showed that in patients with advanced hepatocellular carcinoma, the disease control and response rates of hepatitis-infected and uninfected patients were similar and hepatitis patients did not show a higher tendency of adverse reactions [4]. A retrospective cohort study found that 5.3% of patients had HBV reactivation, which is concerning and cannot be ignored [5].

Therefore, it is crucial to conduct a comprehensive evaluation of ICIs' efficacy and safety in patients with hepatitis B/C for clinical decision-making. Previously published studies are usually retrospective and observational, with only a small number of intervention studies, so we conduct a meta-analysis to combine their results to obtain convincing evidence.

2. Methods

2.1. Search Strategy. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed during this meta-analysis, and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the number CRD42022341247.

2.2. Study Selection. Searches were conducted in PubMed, EMBASE, the Cochrane Library, and Web of Science until October 2022, for studies pertaining to ICIs in tumor patients with hepatitis B or C. The search terms utilized keywords and Medical Subject Headings (MeSH) terms to define conditions such as ICIs, hepatitis B, and hepatitis C. Specific retrieval strategies are presented in Appendix.

Literature screening was carried out by two authors (HJD and CXX) independently by reading the title, abstract, and full text to select the studies eligible for inclusion that met the following inclusion criteria: (1) the type is intervention trial (randomized or nonrandomized and controlled or noncontrolled) or observational study (cohort studies, case-control studies, or case series with more than 5 hepatitis, and prospective or retrospective), (2) participants were treated with ICIs, either alone or in combination with other treatments, (3) the study reported the efficacy of ICIs in tumor patients with hepatitis B or C, with or without safety outcomes, and (4) the study was published in English.

If an update of the same population data was given, the latest literature would be selected. If there was any disagreement during the literature screening, it would be decided after a full discussion with the third researcher (HJC).

2.3. Data Extraction. Two authors (HJD and CXX) extracted the data independently. Incongruities would be resolved by discussions with the third author (HJC). Following are the characteristics of the extracted data in the included studies: authors, year of publication, country, study types, carcinoma, type of hepatitis, ICIs, ICIs types, number of patients, mean age, effective outcomes (mOS, mPFS, ORR, DCR), and security outcome (incidence of adverse reactions). All data were recorded in the table.

2.4. Assessment of Study Quality and Publication Bias. Three tools were used to adjust for different types of studies in this meta-analysis. The Cochrane risk-of-bias tool (RoB 2.0) was used for randomized controlled trials, while Risk Of Bias In Non-randomised Studies of Interventions (ROBINS I) was used for nonrandomized intervention studies. Evaluation of observational studies was done using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). In addition, potential publication bias was assessed by Begg's test.

2.5. Data Analysis. All statistical analyses were conducted using STATA software (version 14.10). A value of $P < 0.05$ was considered statistically significant. Meta-analysis of rates was carried out with Freeman–Tukey double arcsine transformation (metaprop command, ftt option). In order to assess statistical heterogeneity, the I^2 statistic was used. Subsequently, considering the heterogeneity of research design and study types, the meta-analysis was mainly based on a random-effect model. The subgroup analysis was based primarily on the location of the tumor.

3. Results

3.1. Study Selection. As a result of the retrieval strategy, we identified 1840 records, which were subsequently reduced to 1211 after removing duplicate records. Using the title and abstract to assess eligibility, 1012 studies were excluded. Reading 199 studies in their entirety, 24 articles [4, 6–28] were deemed to be eligible for inclusion, including 7 prospective studies and 17 retrospective studies. Finally, 2,625 patients were enrolled, involving 1,179 patients with hepatitis (HBV or HCV). In Figure 1, one can see a detailed description of the retrieval process.

3.2. Study Characteristics. The baseline characteristics of 24 studies are summarized in Supplementary Table S1 and Supplementary Table S2. The inclusion criteria of hepatitis patients in each study are detailed in Supplementary Table S3. Among all the studies included, the efficacy of ICIs in patients with HBV or HCV was evaluated and safety was evaluated in 13 studies. Among 1,179 patients with hepatitis, 11 studies included patients with HBV, 2 studies included patients with HCV, and 11 studies included patients with HBV or HCV. In ICIs, the vast majority was anti-PD-1 or anti-PD-L1 (19), followed by anti-CTLA-4 (4). 1 study was anti-PD-1 combined with anti-CTLA-4, and 1 study did not specify the type of ICIs. The categories of tumors included the following: liver (15), lung (8), melanoma (4), kidney (3), stomach (2), colorectum (1), biliary (1), esophagus (1), head and neck tumor (1), glioblastoma (1), and urothelium (1).

3.3. Clinical Efficacy Response

3.3.1. ORR. A total of 21 studies reported ORR data [4, 6–9, 11–14, 16, 18–28], involving 815 uninfected patients and 1,061 hepatitis patients. This meta-analysis showed (Figure 2) that the pooled ORR of uninfected patients, HCV

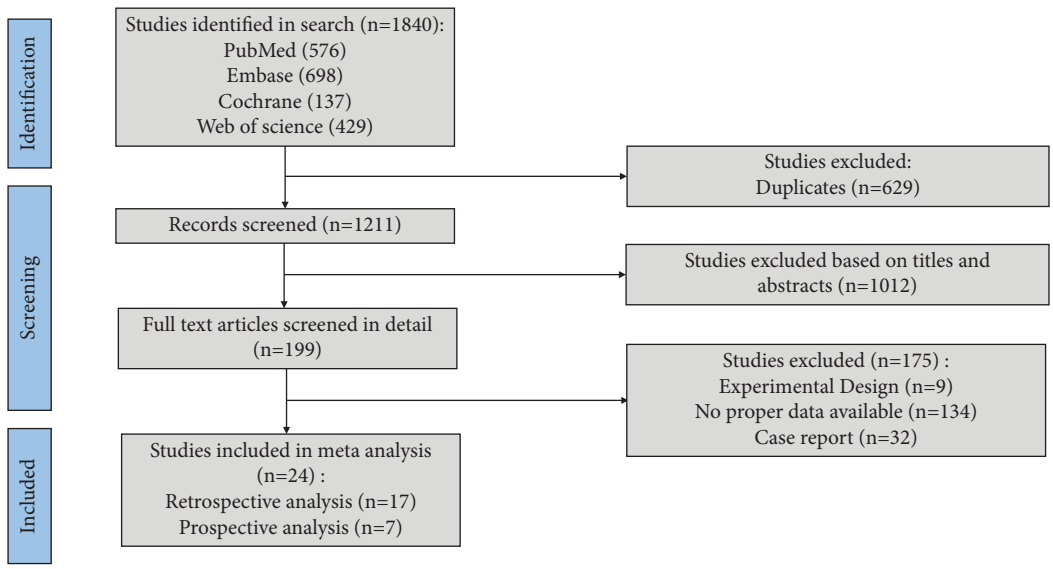


Figure 1: Flow diagram of search and selection.

patients, and HBV patients was 18.10% (95% CI: 12.00%–25.00%), 23.95% (95% CI: 16.36%–32.28%), and 26.49% (95% CI: 21.12%–32.19%), respectively. The pooled ORR of 1,061 hepatitis patients was 25.80% (95% CI: 21.47%–30.35%). In subgroup analysis among hepatitis patients, the liver group showed higher pooled value (25.97%, 95% CI: 21.36%–30.83%) than other tumors group (25.14%, 95% CI: 15.34%–36.12%) (Supplementary Figure 1*). If one study included both liver tumors and other tumors, it would be classified into other tumors group in the subgroup analysis, which was also the same in other analysis.*.

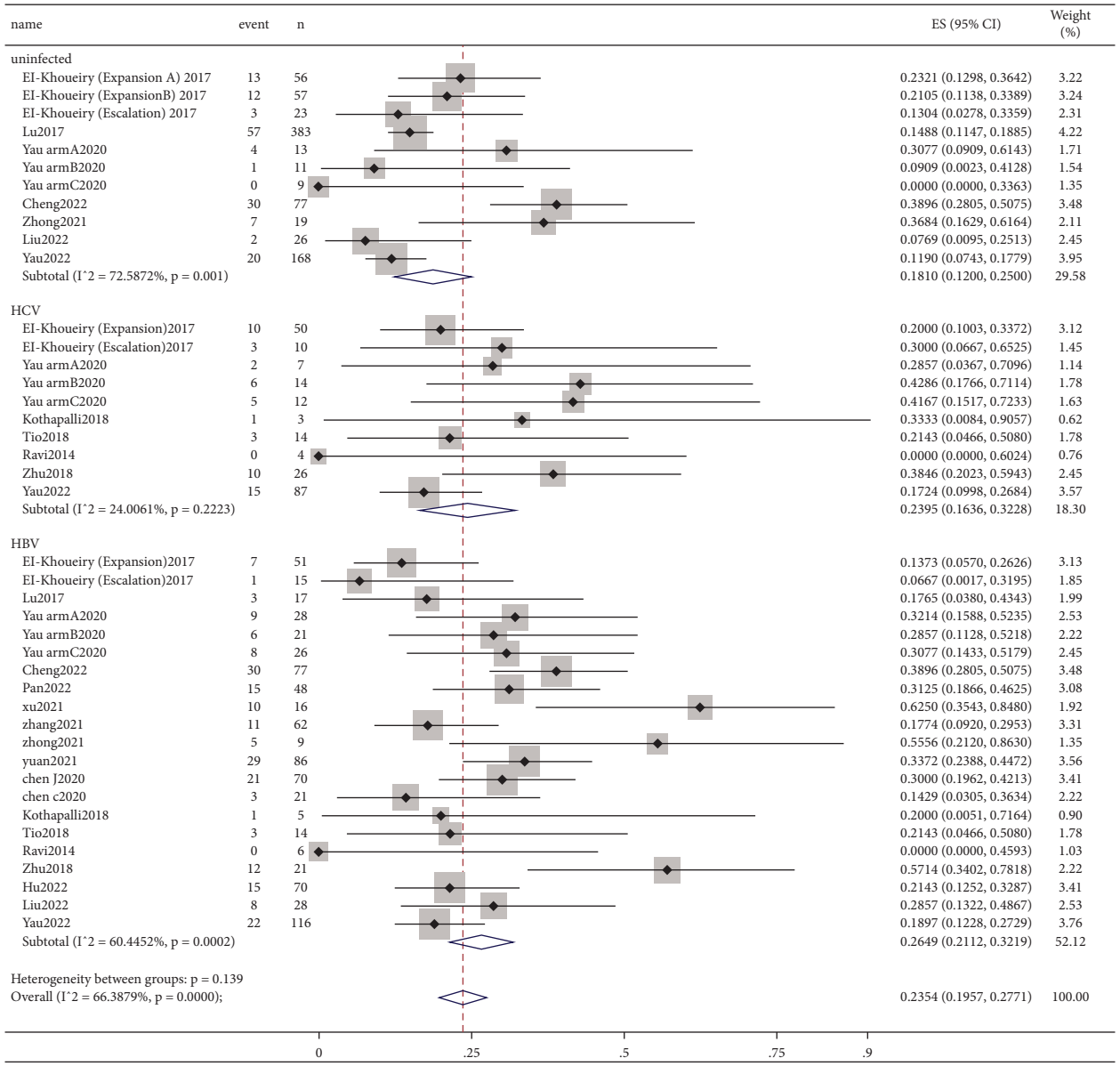
3.3.2. DCR. Fourteen studies included DCR parameters [4, 6–8, 12–14, 16, 20–23, 26, 27]. The pooled DCR of uninfected patients and HCV and HBV patients was 58.74% (95% CI: 46.89%–70.13%), 67.83% (95% CI: 52.01%–82.14%), and 65.79% (95% CI: 58.86%–72.43%). After the merger of 658 patients with hepatitis, the pooled value was 66.22% (95% CI: 60.02%–72.20%). The forest plot is given in Figure 3. According to the subgroup analysis based on the categories of tumors among hepatitis patients, the pooled value of the liver group was 67.67% (95% CI: 62.30%–72.82%), which was higher than other tumors group (64.10%, 95% CI: 49.96%–77.28%) (Supplementary Figure 1).

3.3.3. mPFS. Median progression-free survival (mPFS) was published by 11 studies [8, 9, 12, 15, 17, 19, 20, 22–24, 27]. The pooled mPFS (Figure 4) was 5.01 months (95% CI: 4.05–5.97) for uninfected patients, 5.72 months (95% CI: 2.29–9.15) for patients with HCV, and 4.39 months (95% CI: 2.12–6.66) for patients with HBV. For all patients with hepatitis, the pooled value was 4.94 months (95% CI: 3.29–6.60). In addition, we calculated the mean of mPFS in these four sets of data, which was 4.83 months (uninfected), 5.75 months (HCV), 4.15 months (HBV), and 5.96 months (hepatitis). The pooled value of liver tumors (5.98 months, 95% CI: 3.55–8.42) was longer than that of the other tumors group (4.02 months, 95% CI: 1.73–6.31) of patients with hepatitis (Supplementary Figure 1).

3.3.4. mOS. Median overall survival (mOS) was published by 12 studies [8–12, 15, 17, 19, 20, 22, 23, 27]. According to the meta-analysis, the pooled mOS was 13.30 months (95% CI: 8.24–18.36), 18.29 months (95% CI: −0.61–37.18), 12.90 months (95% CI: 9.85–15.96), and 15.44 months (95% CI: 8.86–22.01) for patients who were uninfected and those who had HCV, HBV, and hepatitis (Figure 5). The pooled mOS of liver tumors was 12.94 months (95% CI: 11.15–14.74), which is shorter than that of the other tumors group (19.37 m, 95% CI: 8.37–30.38) (Supplementary Figure 1). We also calculated the mean of mOS, with values 14.17 m (uninfected), 19.94 m (HCV), 14.67 m (HBV), and 17.17 m (hepatitis), respectively.

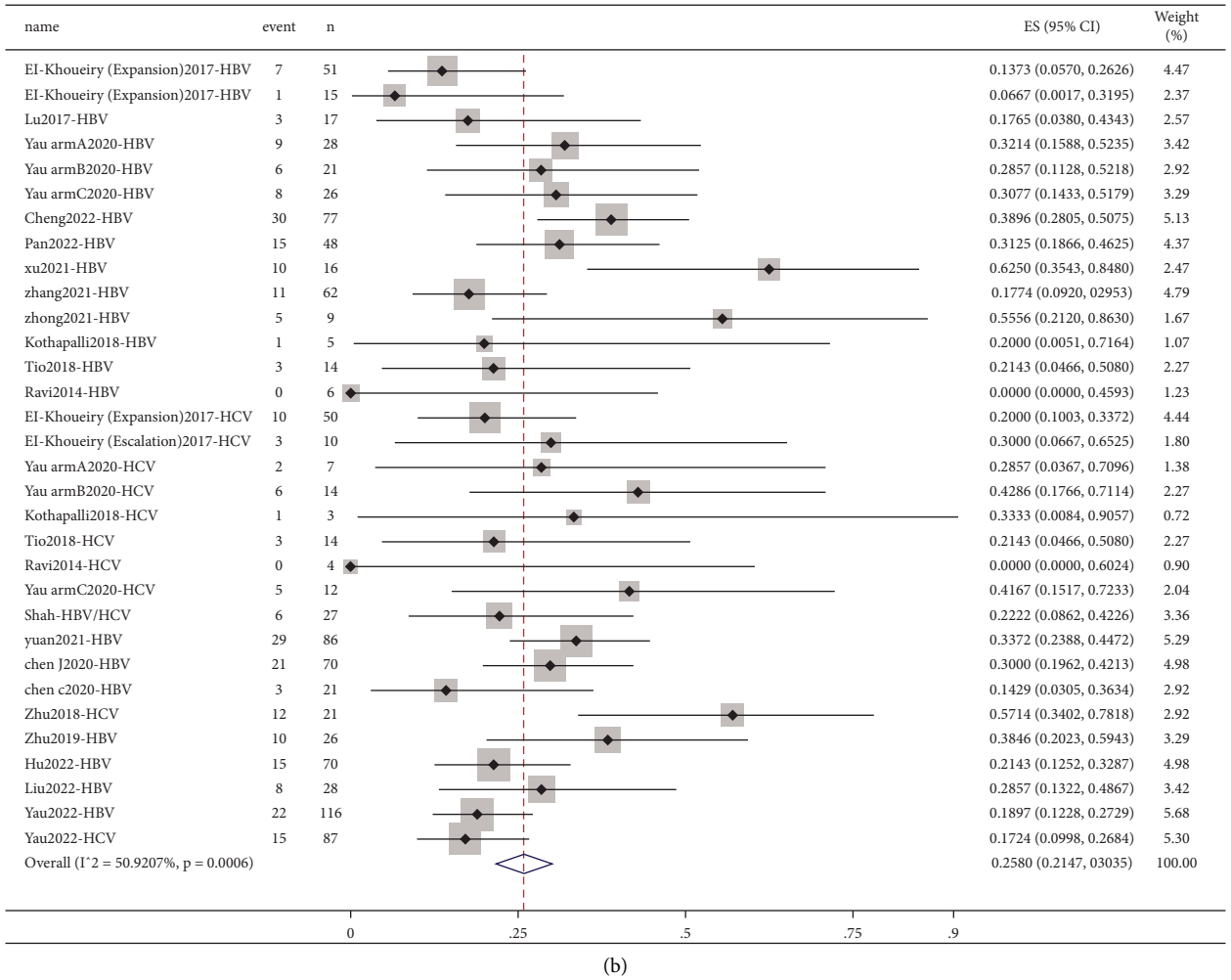
3.4. Adverse Events. The incidence of immune-related adverse events (irAEs) in hepatitis patients and uninfected patients was further combined. A total of 13 studies reported irAEs [4, 7, 8, 10–12, 14, 16, 18–20, 22, 27]. irAEs were classified into all grades and grades 3-4. The highest pooled value of all-grade irAEs was HCV patients (71.53%, 95% CI: 49.66%–89.58%), followed by uninfected patients (70.43%, 95% CI: 51.84%–86.31%), HBV patients (68.33%, 95% CI: 54.78%–80.55%), and hepatitis patients (68.02%, 95% CI: 57.37%–77.87%). Forest plots are presented in Figure 6. The pooled value of the incidence of grade 3-4 irAEs was, respectively, 21.79% (95% CI: 10.48%–35.43%), 32.93% (95% CI: 23.05%–43.53%), 15.18% (95% CI: 7.74%–24.31%), and 21.27% (95% CI: 13.89%–29.61%) in uninfected patients and those who had HCV, HBV, and hepatitis (Figure 7).

Among hepatitis patients, the pooled incidence of all-grade irAEs in the liver group (76.67%, 95% CI: 64.06%–87.45%) was higher than in other tumors group (53.34%,



(a)

Figure 2: Continued.



(b)

Figure 2: Forest plots depicting pooled ORR of (a) uninfected patients and patients with HCV and HBV and (b) patients with hepatitis.

95% CI: 39.35%–67.08%) (Supplementary Figure 2). The pooled value of grade 3-4 irAEs showed similar results: the liver group value was 28.19% (95% CI: 18.48%–38.93%), and the other tumors group value was 12.36% (95% CI: 4.92%–22.04%) (Supplementary Figure 2).

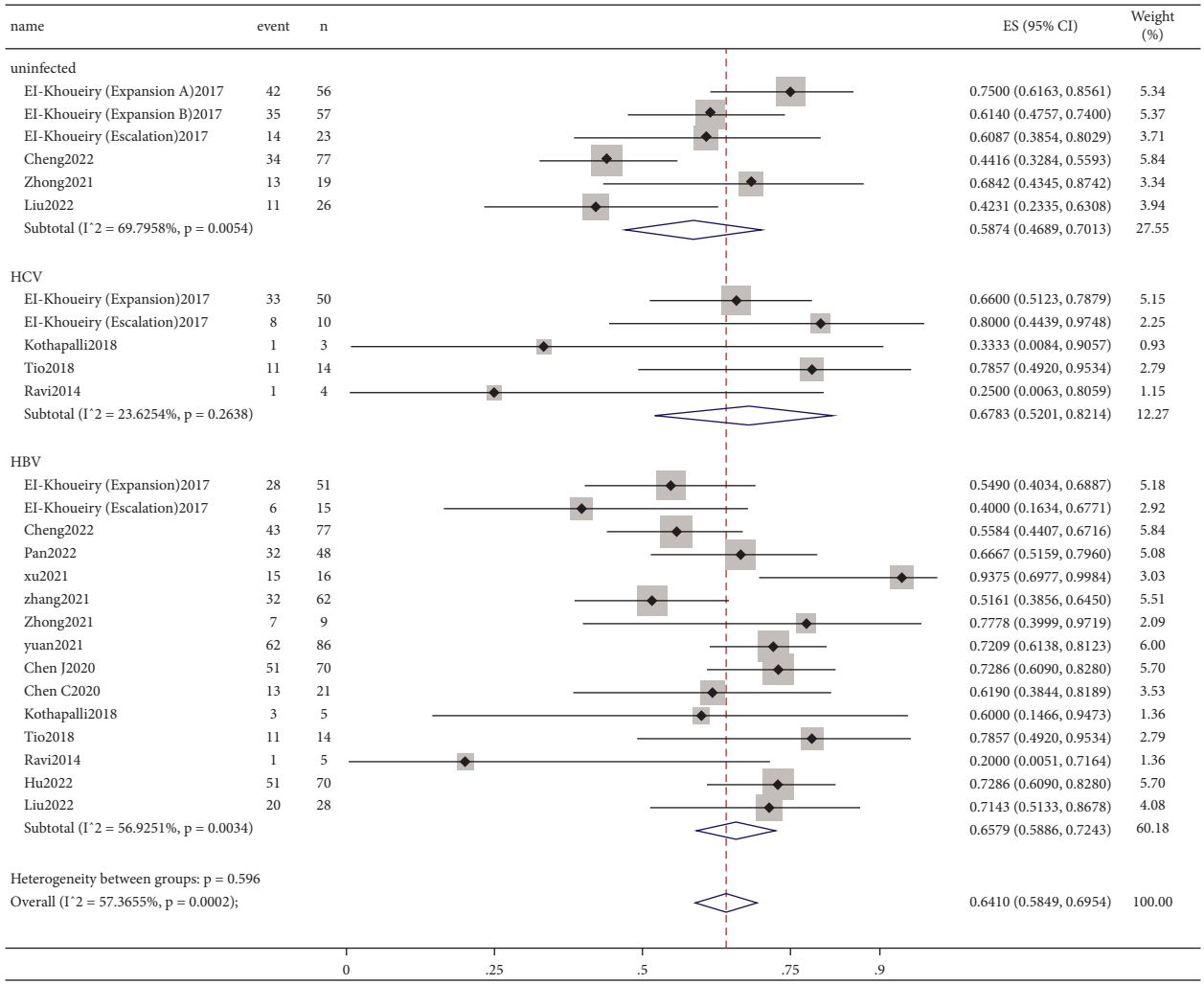
We further analyzed glutamic pyruvic transaminase (ALT) and glutamic oxaloacetic transaminase (AST). Patients with HCV show a higher pooled incidence rate of elevated liver enzymes, both in all-grades and grade 3-4 irAEs. Detailed data are provided in Table 1 and Supplementary Figure 3.

3.5. Subgroup Analysis. In addition to the location of the tumor, we carried out a subgroup analysis of ICI types. The results suggested that the combination of ICIs showed higher ORR and DCR. At the same time, the incidence of irAEs for patients receiving combined therapy of anti-PD-1 and anti-CTLA-4 drugs was higher than that of a single drug (81.27% vs. 59.95%) and the incidence of high-grade irAEs was also higher (34.04% vs. 14.89%). Detailed results are provided in Figure 8. The forest plots are shown in Supplementary Figure 4.

3.6. Quality Assessment and Publication Bias. We evaluated 2 randomized studies with ROB 2.0, 5 nonrandomized intervention studies with ROBINS-I, and 17 observational studies with STROBE. Only one study showed high risk, while others showed low to medium risk (Supplementary Table S4). There was a publication bias in ORR and grade 3-4 irAEs calculated by Begg's test and funnel plots, and others did not show publication bias (Figure 9). Sensitivity analysis indicated that the results were stable, and the detailed results are reported in Supplementary Figure 5.

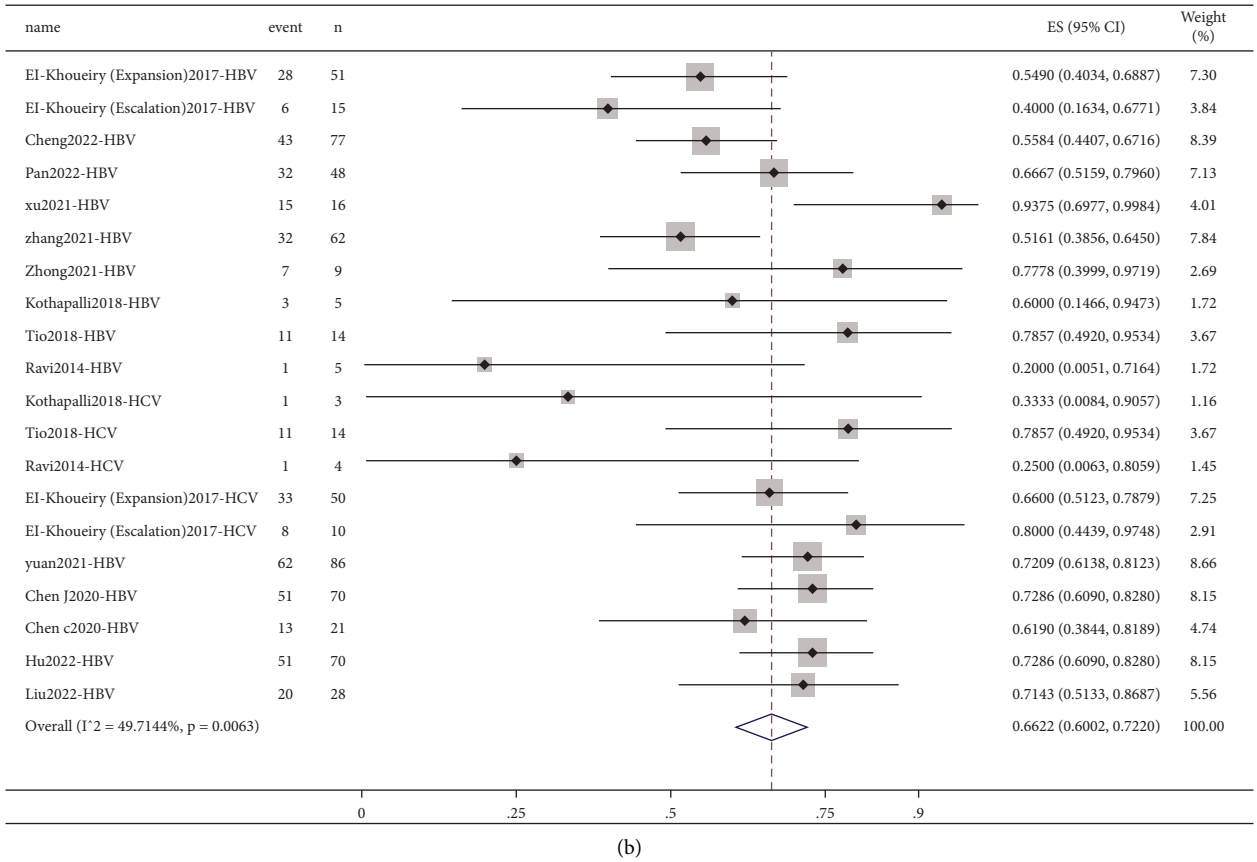
4. Discussion

There has been no systematic review or meta-analysis that evaluated ICIs' efficacy and safety in patients with hepatitis B or C based on the available studies. In our study, we found that ICIs showed higher ORR (25.80% vs. 18.10%) and DCR (66.22% vs. 58.74%) in patients with hepatitis B/C than those without infection. In terms of survival time, patients with hepatitis virus infection showed longer mOS (15.44 m vs. 13.30 m) but shorter mPFS (4.94 m vs. 5.01 m) than uninfected patients. As for safety data, patients with hepatitis showed a lower incidence of all-grade irAEs (68.02% vs.



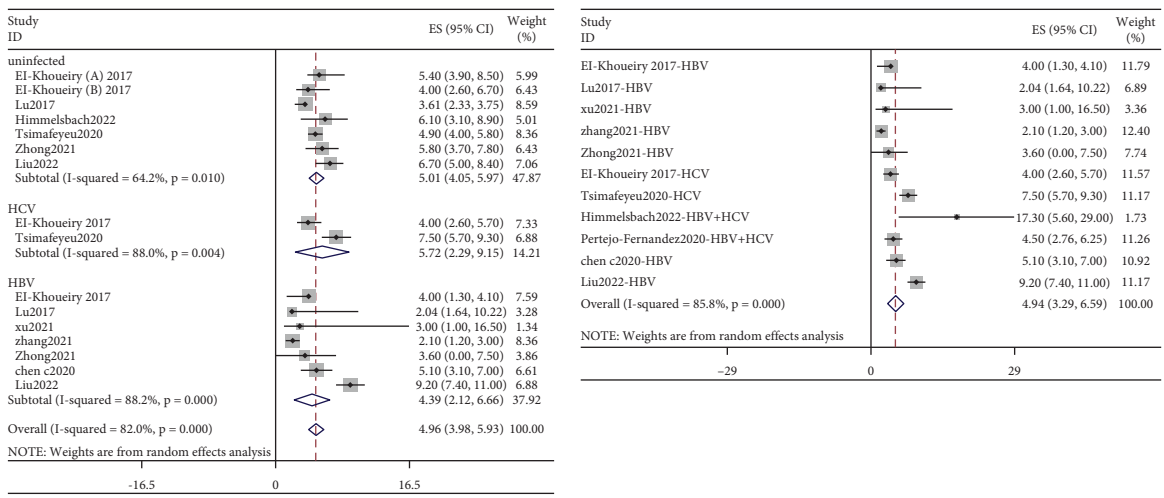
(a)

Figure 3: Continued.



(b)

Figure 3: Forest plots depicting pooled DCR of (a) uninfected patients and patients with HCV and HBV and (b) patients with hepatitis.



(a) (b)

Figure 4: Forest plots depicting pooled mPFS of (a) uninfected patients and patients with HCV and HBV and (b) patients with hepatitis.

70.43%) than uninfected patients, while that of 3-4 irAEs (21.27% vs. 21.79%) was similar in the two groups. However, hepatic dysfunction wasmore common and serious in hepatitis patients.

Immune escape of tumor cells is mediated by the PD-1/PD-L1 axis and CTLA-4. PD-1 is a negative regulatory cell surface receptor and an important regulator of the adaptive immune response, which is expressed in T cells, B cells, macrophages, and so on. Two ligands of PD-1, PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273), can downregulate the effector function of T cells by binding to PD-1 [29]. CTLA-4 is a member of a family of immunoglobulin-related receptors, which is predominantly found in intracellular vesicles in FoxP3 regulatory T cells (Tregs) or activated

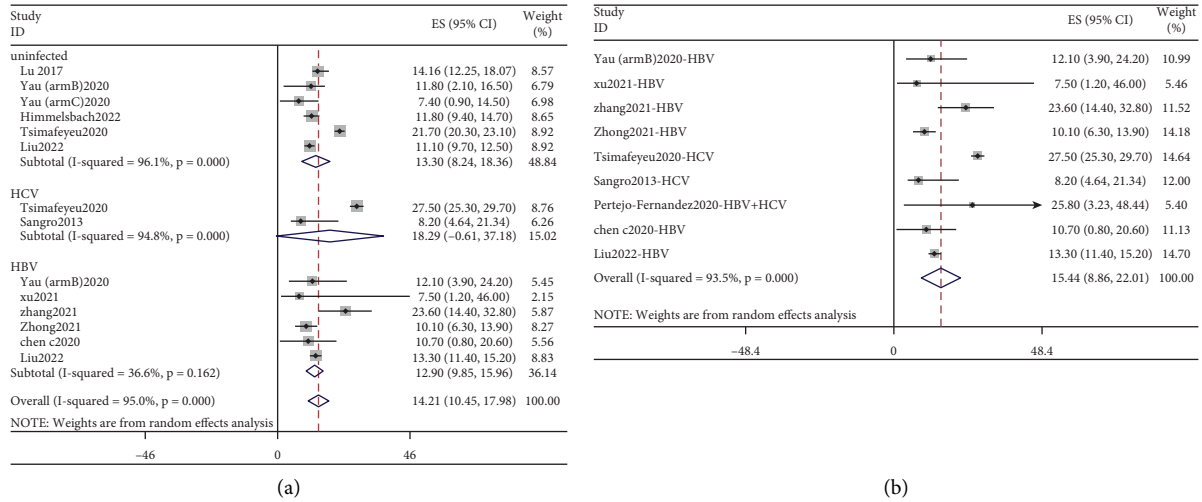


Figure 5: Forest plots depicting pooled mOS of (a) uninfected patients and patients with HCV and HBV and (b) patients with hepatitis.

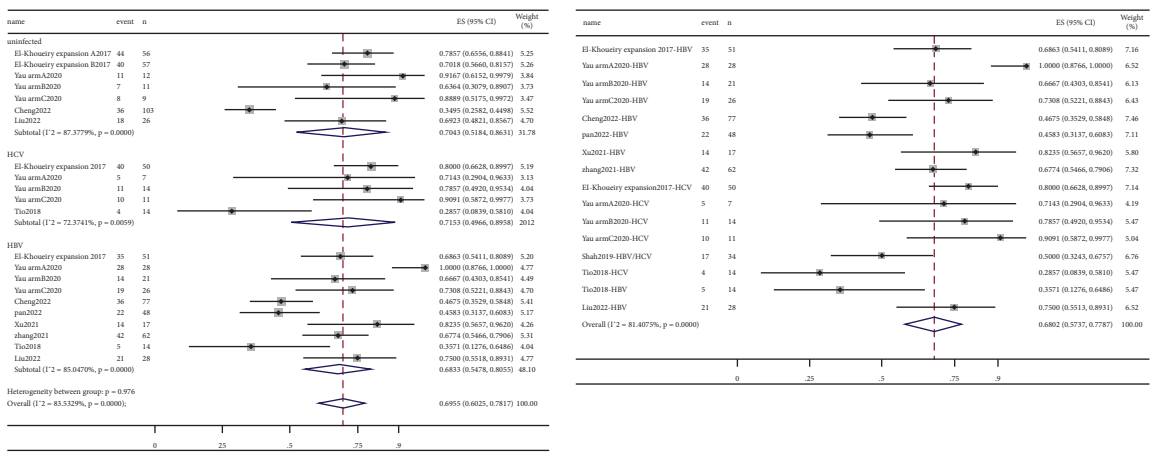


Figure 6: Forest plots depicting the pooled value of all-grade irAEs of (a) uninfected patients and patients with HCV and HBV and (b) patients with hepatitis.

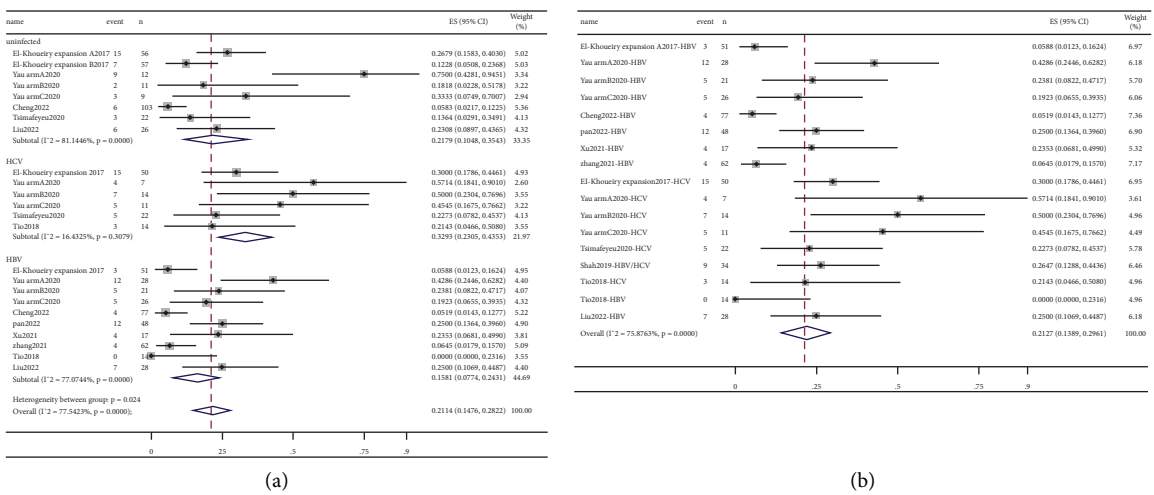


Figure 7: Forest plots depicting the pooled value of grade 3-4 irAEs of (a) uninfected patients and patients with HCV and HBV and (b) patients with hepatitis.

Table 1: The pooled incidence rate of AST and ALT abnormalities.

Characteristics		Incidence (%)	95% CI	P	I^2 (%)
AST increase					
All grades	Uninfected	14.17	5.18%–25.86%	0.086	51.01
	HCV	24.20	4.79%–50.46%	<0.001	83.11
	HBV	12.26	5.61%–20.71%	0.026	60.63
	Hepatitis	16.93	8.32%–27.45%	<0.001	76.97
Grades 3-4	Uninfected	3.16	0.01%–9.43%	0.211	31.57
	HCV	17.37	5.51%–32.96%	0.043	59.43
	HBV	3.09	0.34%–7.56%	0.121	42.57
	Hepatitis	7.69	2.30%–15.13%	<0.001	71.08
ALT increase					
All grades	Uninfected	8.56	1.49%–19.19%	0.096	52.79
	HCV	36.07	11.45%–64.51%	<0.001	79.99
	HBV	13.07	5.62%–22.48%	0.041	56.84
	Hepatitis	21.27	10.91%–33.49%	0.210	33.65
Grades 3-4	Uninfected	2.25	0.00%–8.19%	0.293	19.17
	HCV	9.39	2.19%–19.43%	0.409	1.10
	HBV	0.95	0.00%–3.66%	0.044	46.65
	Hepatitis	3.48	0.37%–8.46%	0.210	33.65

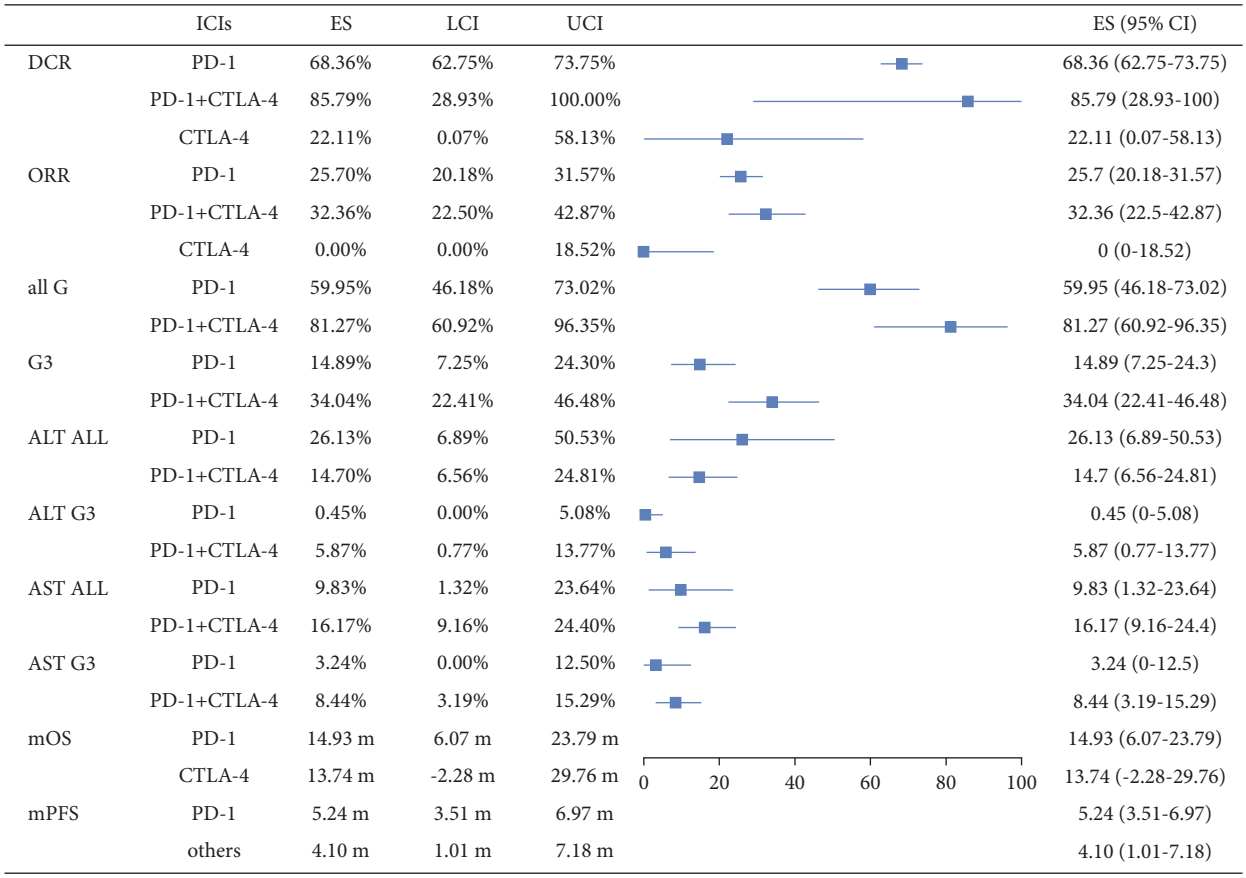


Figure 8: The subgroup analysis of ICI types.

conventional T cells. CTLA-4 is homologous to T-cell costimulatory protein CD28 and shares two ligands, namely, CD80 and CD86. The interaction between ligands and CTLA-4 is helpful to inhibit T-cell response [30]. ICIs can restore T-cell function by blocking the binding of PD-1 or CTLA-4 to ligands, thus achieving the purpose of tumor therapy. However, in patients with hepatitis B/C, this situation becomes complicated.

There has been evidence that PD-1 was significantly overexpressed on total and HCV-specific CD8 cytotoxic T

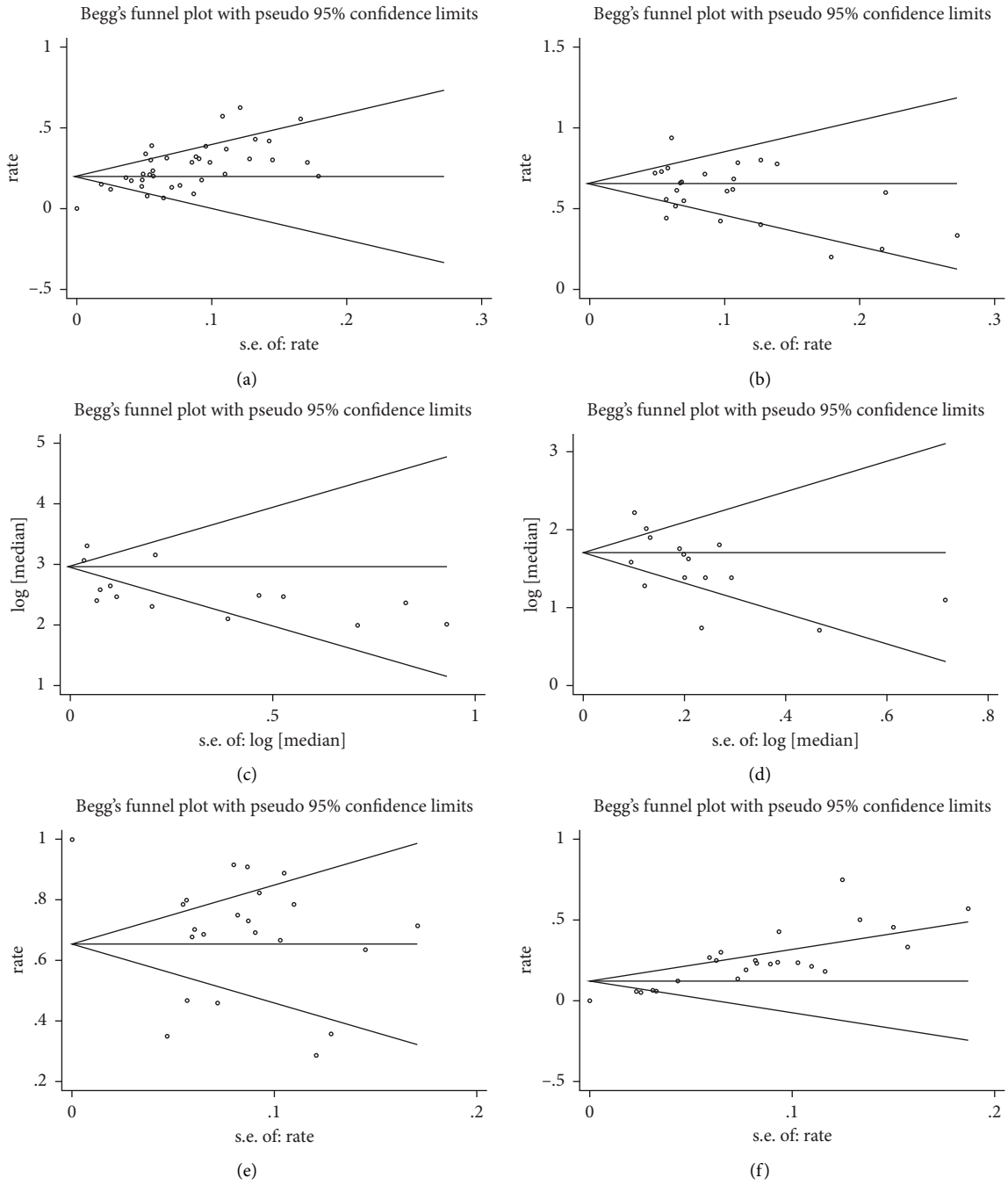


Figure 9: Begg's funnel plots. (a) ORR. (b) DCR. (c) mOS. (d) mPFS. (e) All-grade irAEs. (f) Grade 3-4 irAEs.

lymphocytes (CTLs) in the liver and peripheral blood of patients with persistent HCV infection [31]. Similarly, HBV-specific T cells in the peripheral blood of patients with chronic HBV infection also express high levels of PD-1 [32]. In addition to PD-1, the upregulation of CTLA-4 on virus-specific T cells from chronic HBV and HCV was likewise repeatedly observed [33]. Under the action of negative costimulatory molecules such as CTLA-4 and PD-1, specific T-cell dysfunction occurs in patients with persistent hepatitis B or C infection. Therefore, while blocking this process to inhibit tumors, ICIs may also reverse T-cell depletion and play an antiviral effect, which has been observed in some clinical studies. El-Khoueiry [8] observed a transient decrease of hepatitis C virus RNA in some patients infected with HCV, showing limited antiviral activity of nivolumab. Sangro [10] identified a decrease in viral load after treatment with tremelimumab and a transient complete viral response in three patients during follow-up. According to a recent study, this antiviral effect may be related to ICIs' effects on Tregs, which plays an important role in HBV and HCV patients [34].

In addition, Han found that serum-soluble PD-L1 (sPD-L1) levels in patients with HBV-related hepatocellular carcinoma (HCC) was markedly increased, which was positively correlated with the expression of PD-L1 in tumor tissues [35]. The upregulation of PD-L1 was also observed in patients with HCV infection [36]. In view of the fact that the expression level of PD-L1 in tumor tissues has become a biomarker for predicting the efficacy of immunotherapy [37], it can be speculated that the high ORR and DCR of ICIs in patients with HCV/HBV are related to the high expression of PD-L1.

However, ICIs may also weaken the ability of T cells to inhibit viral hepatitis, resulting in HBV/HCV reactivation [6]. The incidence of HBV reactivation (HBVr) and HCV reactivation (HCVr) induced by immunotherapy is not clear. Among the 878 hepatitis patients we included, 4 HBVr and no HCVr were observed [16, 22, 26], so we thought that the probability of hepatitis reactivation caused by ICIs was relatively low. In addition to HBVr and HCVr, immune-mediated hepatotoxicity constitutes one of the reasons why researchers exclude clinical trials because hepatitis patients are often accompanied by baseline damage of liver function. Immune-mediated hepatic dysfunction was found to be more common and severe in patients with hepatitis than in patients without infection, according to our study. In HBV patients, this is more prevalent than in HCV patients. The reason for this might be that patients with HCV have a higher risk of suffering from liver damage (micronodular cirrhosis, lymphoid aggregates, damage to the bile ducts, etc.) than those with HBV [38]. Meanwhile, in the subgroup analysis, the incidence of immune-mediated hepatic dysfunction was higher in those given the combination of anti-PD-1 and anti-CTLA-4, both in all grades and high grades (except the incidence of ALT increases in all grades).

There are certain limitations that originated from the finite number of studies present in this meta-analysis. The literature included in this study is dominated by observational studies. Therefore, the interpretation still needs to be further verified by larger samples and randomized clinical trials. In addition, the majority of patients in related studies were diagnosed with liver cancer, possibly because HBV/HCV and liver cancer are closely related, which may lead to a certain bias. In addition, due to the lack of analysis of viral hepatitis stages in many studies, there was no subgroup analysis of this factor.

5. Conclusion

According to this meta-analysis, ICIs in patients with hepatitis B or C are effective and safe, but the baseline of liver enzyme should be evaluated before use, especially when multiple ICIs are used in combination. Besides, the infectious disease physician should be invited to evaluate and follow up the patients.

Data Availability

Detailed information about the original contributions to the study is included within the article/Supplementary Materials. Further data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

All authors participated in the development and execution of the analysis plan. The hypothesis and idea for the systematic review were proposed by HD and CX. HD and CX conducted the literature search and reviewed studies for inclusion in the report. Data extraction and check were done by XZ and YZ. HD, CX, and YZ conducted all meta-analyses and wrote this paper. All authors contributed to the article and approved its submission.

Acknowledgments

This work was funded by Capital's Funds for Health Improvement and Research (No. 2022-2-4065), National High Level Hospital Clinical Research Funding (2022-NHLHCRF-LX-02-0111), and China-Japan Friendship Hospital.

Supplementary Materials

The following supporting information can be obtained from Supplementary Materials: Appendix: search strategy; Table S1: basic characteristics of the included studies; Table S2: immune-related adverse reactions of the included studies; Table S3: HCV/HBV inclusion criteria of the included studies; Table S4: risk of bias assessment; Figure S1: subgroup analysis of ORR, DCR, mPFS, and mOS; Figure S2: subgroup analysis of all-grade irAEs and grade 3-4 irAEs; Figure S3: the pooled incidence rate of AST, ALT abnormalities; Figure S4: the subgroup analysis of ICIs; Figure S5: the sensitivity analysis. (*Supplementary Materials*)

References

[1] M. E. Himmel, S. D. Saibil, and A. P. Saltman, "Immune checkpoint inhibitors in cancer immunotherapy," *Canadian Medical Association Journal*, vol. 192, no. 24, p. E651, 2020.

[2] J. M. Pawlotsky, F. Negro, A. Aghemo et al., "EASL recommendations on treatment of hepatitis C: final update of the series," *Journal of Hepatology*, vol. 73, no. 5, pp. 1170–1218, 2020.

[3] M. H. Nguyen, G. Wong, E. Gane, J. H. Kao, and G. Dusheiko, "Hepatitis B virus: advances in prevention, diagnosis, and therapy," *Clinical Microbiology Reviews*, vol. 33, no. 2, pp. 000466–19, 2020.

[4] A. Kothapalli and M. A. Khattak, "Safety and efficacy of anti-PD-1 therapy for metastatic melanoma and non-small-cell lung cancer in patients with viral hepatitis: a case series," *Melanoma Research*, vol. 28, no. 2, pp. 155–158, 2018.

[5] X. Zhang, Y. Zhou, C. Chen et al., "Hepatitis B virus reactivation in cancer patients with positive Hepatitis B surface antigen undergoing PD-1 inhibition," *Journal For Immunotherapy of Cancer*, vol. 7, no. 1, p. 322, 2019.

[6] S. Ravi, K. Spencer, M. Ruisi et al., "Ipilimumab administration for advanced melanoma in patients with pre-existing Hepatitis B or C infection: a multicenter, retrospective case series," *Journal for ImmunoTherapy of Cancer*, vol. 2, no. 1, p. 33, 2014.

[7] M. Tio, R. Rai, O. M. Ezeoke et al., "Anti-PD-1/PD-L1 immunotherapy in patients with solid organ transplant, HIV or hepatitis B/C infection," *European Journal of Cancer*, vol. 104, pp. 137–144, 2018.

[8] A. B. El-Khoueiry, B. Sangro, T. Yau et al., "Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial," *Lancet*, vol. 389, no. 10088, pp. 2492–2502, 2017.

[9] S. Lu, L. Zhang, Y. Cheng et al., "P1.04-010 CheckMate 870: an open-label safety study of nivolumab in previously treated patients with non-small cell lung cancer in asia," *Journal of Thoracic Oncology*, vol. 12, no. 11, p. 1976, 2017.

[10] B. Sangro, C. Gomez-Martin, M. De La Mata et al., "A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C," *Journal of Hepatology*, vol. 59, no. 1, pp. 81–88, 2013.

[11] T. Yau, Y. K. Kang, T. Y. Kim et al., "Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib the CheckMate 040 randomized clinical trial," *JAMA Oncology*, vol. 6, no. 11, Article ID e204564, 2020.

[12] C. Chen, L. An, Y. Cheng, X. Luo, Z. Li, and X. Liu, "Clinical outcomes and prognosis factors of nivolumab plus chemotherapy or multitarget tyrosine kinase inhibitor in multi-line therapy for recurrent hepatitis B virus-related hepatocellular carcinoma: a retrospective analysis," *Frontiers in Oncology*, vol. 10, p. 1404, 2020.

[13] J. Chen, X. Hu, Q. Li et al., "Effectiveness and safety of toripalimab, camrelizumab, and sintilimab in a real-world cohort of hepatitis B virus associated hepatocellular carcinoma patients," *Annals of Translational Medicine*, vol. 8, no. 18, p. 1187, 2020.

[14] Y. K. Cheng, P. Chen, D. W. Chen, S. B. Ye, and P. Lan, "Comparative safety, efficacy and survival outcome of anti-PD-1 immunotherapy in colorectal cancer patients with vs. without hepatitis B virus infection: a multicenter cohort study," *Clinical and Translational Gastroenterology*, vol. 13, no. 5, Article ID e00475, 2022.

[15] V. Himmelsbach, M. Pinter, B. Scheiner et al., "Efficacy and safety of atezolizumab and bevacizumab in the real-world treatment of advanced hepatocellular carcinoma: experience from four tertiary centers," *Cancers*, vol. 14, no. 7, p. 1722, 2022.

[16] S. Pan, Y. Yu, S. Wang et al., "Correlation of HBV DNA and hepatitis B surface antigen levels with tumor response, liver function and immunological indicators in liver cancer patients with HBV infection undergoing PD-1 inhibition combinational therapy," *Frontiers in Immunology*, vol. 13, Article ID 892618, 2022.

[17] A. Pertejo-Fernandez, B. Ricciuti, S. P. Hammond et al., "Safety and efficacy of immune checkpoint inhibitors in patients with non-small cell lung cancer and hepatitis B or hepatitis C infection," *Lung Cancer*, vol. 145, pp. 181–185, 2020.

[18] N. J. Shah, G. Al-Shbool, M. Blackburn et al., "Abstract 3230: safety and efficacy of immune checkpoint inhibitors (ICIs) in patients with HIV, hepatitis B, or hepatitis C viral infections," *Cancer Research*, vol. 79, p. 3230, 2019.

[19] I. Tsimafeyeu, R. Gafanov, S. Protsenko et al., "Nivolumab in patients with metastatic renal cell carcinoma and chronic hepatitis C virus infection," *Cancer Immunology Immunotherapy*, vol. 69, no. 6, pp. 983–988, 2020.

[20] F. Xu, Z. Zeng, B. Yan et al., "Safety and efficacy of anti-PD-1 inhibitors in Chinese patients with advanced lung cancer and hepatitis B virus infection: a retrospective single-center study," *Translational Lung Cancer Research*, vol. 10, no. 4, pp. 1819–1828, 2021.

[21] G. S. Yuan, R. Li, Q. Li et al., "Interaction between hepatitis B virus infection and the efficacy of camrelizumab in combination with apatinib therapy in patients with hepatocellular carcinoma: a multicenter retrospective cohort study," *Annals of Translational Medicine*, vol. 9, no. 18, p. 1412, 2021.

[22] X. Y. Zhang, D. Tian, Y. Chen et al., "Association of hepatitis B virus infection status with outcomes of non-small cell lung cancer patients undergoing anti-PD-1/PD-L1 therapy," *Translational Lung Cancer Research*, vol. 10, no. 7, pp. 3191–3202, 2021.

[23] L. T. Zhong, P. S. Zhong, H. F. Liu, Z. Li, Q. Nie, and W. Peng, "Hepatitis B virus infection does not affect the clinical outcome of anti-programmed death receptor-1 therapy in advanced solid malignancies Real-world evidence from a retrospective study using propensity score matching," *Medicine*, vol. 100, no. 49, Article ID e28113, 2021.

[24] R. K. Kelley, P. M. Bracci, B. Keenan et al., "Pembrolizumab (PEM) plus granulocyte macrophage colony stimulating factor (GM-CSF) in advanced biliary cancers (ABC): final outcomes of a phase 2 trial," *Journal of Clinical Oncology*, vol. 40, p. 444, 2022.

[25] A. X. Zhu, R. S. Finn, J. Edeline et al., "Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial," *The Lancet Oncology*, vol. 19, no. 7, pp. 940–952, 2018.

[26] X. Hu, R. Li, Q. Li, M. Zang, G. Yuan, and J. Chen, "Interaction between baseline HBV loads and the prognosis of patients with HCC receiving anti-PD-1 in combination with antiangiogenic therapy undergoing concurrent TAF prophylaxis," *BMC Infectious Diseases*, vol. 22, no. 1, p. 614, 2022.

[27] H. Liu, X. Qin, Z. Xu et al., "Comparison of effectiveness and safety of camrelizumab between HBV-related and non-B, non-C hepatocellular carcinoma: a retrospective study in China," *Frontiers in Genetics*, vol. 13, Article ID 1000448, 2022.

[28] T. Yau, J. W. Park, R. S. Finn et al., "Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial," *The Lancet Oncology*, vol. 23, no. 1, pp. 77–90, 2022.

[29] J. A. Seidel, A. Otsuka, and K. Kabashima, "Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations," *Frontiers in Oncology*, vol. 8, p. 86, 2018.

[30] B. Rowshanravan, N. Halliday, and D. M. Sansom, "CTLA-4: a moving target in immunotherapy," *Blood*, vol. 131, no. 1, pp. 58–67, 2018.

[31] L. Golden-Mason, B. Palmer, J. Klarquist, J. A. Mengshol, N. Castelblanco, and H. R. Rosen, "Upregulation of PD-1 expression on circulating and intrahepatic hepatitis C virus-specific CD8+ T cells associated with reversible immune dysfunction," *Journal of Virology*, vol. 81, no. 17, pp. 9249–9258, 2007.

[32] C. Boni, P. Fisicaro, C. Valdatta et al., "Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic

HBV infection," *Journal of Virology*, vol. 81, no. 8, pp. 4215–4225, 2007.

[33] H. Cho, H. Kang, H. H. Lee, and C. Kim, "Programmed cell death 1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) in viral hepatitis," *International Journal of Molecular Sciences*, vol. 18, no. 7, p. 1517, 2017.

[34] A. Granito, L. Muratori, C. Lalanne et al., "Hepatocellular carcinoma in viral and autoimmune liver diseases: role of CD4+ CD25+ Foxp3+ regulatory T cells in the immune microenvironment," *World Journal of Gastroenterology*, vol. 27, no. 22, pp. 2994–3009, 2021.

[35] X. Han, Y.-K. Gu, S.-L. Li, and H. Chen, "Pre-treatment serum levels of soluble programmed cell death-ligand 1 predict prognosis in patients with hepatitis B-related hepatocellular carcinoma," *Journal of Cancer Research and Clinical Oncology*, vol. 145, no. 2, pp. 303–312, 2019.

[36] G. Schönrich and M. J. Raftery, "The PD-1/PD-L1 Axis and virus infections: a delicate balance," *Frontiers in Cellular and Infection Microbiology*, vol. 9, p. 207, 2019.

[37] P. Darvin, S. M. Toor, V. Sasidharan Nair, and E. Elkord, "Immune checkpoint inhibitors: recent progress and potential biomarkers," *Experimental and Molecular Medicine*, vol. 50, no. 12, pp. 1–11, 2018.

[38] R. Rozario and B. Ramakrishna, "Histopathological study of chronic hepatitis B and C: a comparison of two scoring systems," *Journal of Hepatology*, vol. 38, no. 2, pp. 223–229, 2003.