Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 6

Efficacy and Safety of Immune Monotherapy or Immune-Based Combination Therapy Compared with Sorafenib in First-Line Treatment of Advanced Hepatocellular Carcinoma: A Meta-Analysis

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Received: 15 May 2023
Accepted: 22 June 2023
Published: 30 June 2023
J Short Name: COO

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Citation:

Gao X and Huang G, Efficacy and Safety of Immune Monotherapy or Immune-Based Combination Therapy Compared with Sorafenib in First-Line Treatment of Advanced Hepatocellular Carcinoma: A Meta-Analysis. Clin Onco. 2023; 6(24): 1-12

Keywords:

Hepatocellular carcinoma; Immunotherapy; Immune checkpoint inhibitors; Sorafenib; Efficacy; Safety

1. Abstract

With the application and promotion of Immune Checkpoint Inhibitors (ICIs) in advanced hepatocellular carcinoma (HCC), their efficacy and safety are uneven. The purpose of the study is to compare the efficacy and safety of immune monotherapy or immune-based combination therapy compared with sorafenib in the first-line treatment of advanced HCC. We searched PubMed, Embase, and Cochrane Library databases for eligible Phase II or III randomized controlled trials (RCTs) from 2015 to April 2023. HR and its 95% confidence interval (CI) were used to analyze progression-free survival (PFS) and overall survival (OS), OR and its 95% CI were used to analyze objective response rate (ORR), treatment-related adverse events (TRAEs), grade 3-4 TRAEs, and treatment-related serious adverse events (TRSAEs). The study included 7 RCTs with 4852 patients. The results show that, compared with sorafenib, immune monotherapy can benefit patients from OS (HR=0.85, 95% CI: 0.77-0.94, P=0.002) and ORR (OR=2.98, 95% CI: 2.20-4.02, P<0.001), and the safety is good. Combined immunotherapy not only prolonged patients' PFS (HR=0.65, 95% CI: 0.51-0.81, P<0.001), the benefit was more skewed to patients with hepatitis B virus (HBV) infection and alpha-fetoprotein (AFP)<400ug/ml, but also prolonged patients' OS (HR=0.71, 95% CI: 0.64-0.79, P<0.001), the benefit was more skewed to patients with HBV infection and extrahepatic metastases(EHS), and also significantly improved patients' ORR(OR=4.38, 95% CI: 3.34-5.76, P<0.001), the overall adverse reactions are controllable, but it will increase the incidence of TRSAEs (OR=1.98, 95% CI: 1.54-2.54, P<0.001).

2. Introduction

According to the results of the International Agency for Research on Cancer (IARC) [1] new cases of liver cancer in the world in 2020 was 905,700, ranking sixth in the cancer spectrum, the number of deaths reached 830,200, ranking third in the cancer spectrum. There may be 1.4 million new cases of liver cancer diagnosed globally (55.0% increase from 2020) and 1.3 million deaths from liver cancer (56.4% increase from 2020) by 2040 [2]. At present, the main pathological types of liver cancer include hepatocellular

carcinoma (HCC) and intrahepatic cholangiocarcinoma, of which HCC accounts for the total cases 75%-85% of the number. The main risk factors for HCC are viral infection, chronic drinking, metabolic syndrome, or diabetes-related nonalcoholic steatohepatitis (NASH) [3]. Early HCC patients can be cured by radical hepatectomy, liver transplantation, intervention, etc [4]. The main treatment modality for patients with advanced HCC is targeted therapy, chemotherapy, or symptomatic therapy. In the SHARP study [5] median OS of sorafenib in patients with advanced liver cancer was extended to 10.7 months, compared with the placebo it was extended for only 2.8 months; In the EACH study [6] chemotherapy with oxaliplatin only extended the median OS to 5.9 months in patients with advanced HCC, it does not significantly prolong survival and leads to a higher proportion of treatment-related adverse events (TRAEs). Therefore, there is an urgent need for therapeutic methods to improve patients' efficacy and safety. Tumor immunotherapy can improve the efficacy of patients, reduce the toxic side effects of patients, and have obvious advantages in replacing chemotherapy, radiotherapy and targeted drug therapy, which will provide new means for the treatment of tumors.

Common immune checkpoint inhibitors (ICIs) include programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors, and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitors, the corresponding immune checkpoints are PD-1and CTLA-4. Among them, PD-1 blocks TCR signaling inhibits T cell proliferation and secretion of cytotoxic mediators, and the sustained effect will lead to T cell failure [7], and PD-1/PD-L1 inhibitors can prevent tumor immune escape and achieve immune normalization. CTLA-4 is expressed on the surface of activated immune cells and T cells, it competitively binds to the T cell-activating receptor CD28, reducing T cell activation, CTLA-4 inhibitors can lead to a broad enhancement of the immune response dependent on helper T cells [8]. In addition, simultaneous blocking of CTLA-4 and PD-1 or PD-L1 pathways is capable of producing a range of immune stimulation effects distinct from monotherapy, including unique regulation of end-differentiation effector CD8+ T cells [9]. In addition to activating the immune system to produce an anti-tumor immune response, ICIs can also modify the tumor microenvironment (TME) by regulating the immune response, and play an anti-tumor therapeutic effect [10]. Antiangiogenic drug therapy can fully reprogram immunosuppressive TME into immunostimulatory manifestations, thereby enhancing the efficacy of antitumor therapy, reducing the dose required for treatment, and reducing the adverse effects of combination immunotherapy [11-13].

In recent years, with the breakthrough of immunotherapy in other cancers, various clinical trials in HCC have gradually been launched. Due to the high cost and incidence of TRAEs, it is important to evaluate the efficacy and safety of immunotherapy in clinical applications and to explore the dominant population and predictors of clinical benefit. Therefore, we conducted a meta-analysis of clinical trials of first-line therapy for advanced HCC reported worldwide to evaluate the efficacy and safety of immune monotherapy or combined immunotherapy in advanced HCC, and further explore the dominant population of immunotherapy and predictive biomarkers, to provide a more reliable theoretical basis for first-line therapy for patients with advanced HCC.

3. Materials and Methods

3.1. Retrieve the Policy

II or III randomized controlled trials (RCTs) that ICIs-containing therapy compared with sorafenib in the first-line therapy of advanced HCC were examined in PubMed, EMBASE, and Cochrane Library databases from January 2015 to April 2023. At the same time, the abstracts of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) meetings were reviewed to obtain further relevant original research. The studies were selected strictly according to the inclusion and exclusion criteria. The search strategy was constructed according to the PICOS model, and the relevant clinical questions were decomposed to determine the relevant subject terms and freedom. The search strategies are provided as Supplementary material.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria: 1. Subjects: first-line therapy for unresectable, advanced HCC. 2. Interventions versus controls: experimental group: immune monotherapy or immunotherapy combination; control group: sorafenib. 3. Outcomes: progression-free survival(PFS), objective remission rate (ORR), overall survival(OS), TRAEs, grade 3 to 4 TRAEs, and treatment-related serious adverse effects (TRSAEs). 4. Type of Study: RCTs, regardless of whether the clinical study was blinded.

Exclusion Criteria: Reviews, case reports, non-clinical studies, non-randomized controlled clinical studies, studies for which data were not available, studies that were not first-line treatments, etc.

3.3. Literature Quality Evaluation

Two researchers independently searched and read the literature, then excluded the literature without inclusion criteria strictly, further read the whole literature in detail, decide which literature should be included, and finally extract relevant research data after comprehensive analysis. The quality of the literature of the included studies was assessed using the Cochrane Risk of Bias Assessment Tool[14]. Use Review Manager 5 4.0 Software assessed the content of included RCTs (Figure 1).

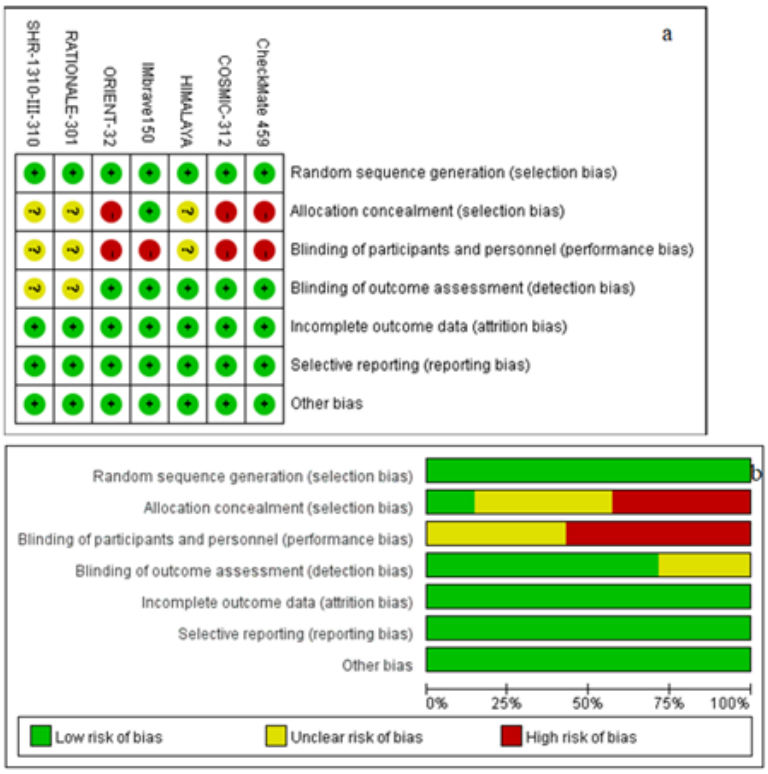

Figure 1: The Cochrane risk Bias assessment tool
(a) Risk of bias graph. (b) Risk of bias summary

3.4. Statistical Analysis

Statistical software STATA17.0 was used to analyze the extracted data. HR and its 95% confidence interval (CI) were used as effect analysis statistics for PFS and OS. OR and its 95%CI were used as effect analysis statistics for ORR, TRAEs, Grade 3-4 TRAEs, and TRSAEs, and were represented by forest maps. Cochran's Q test and I^2 statistics were used as the basis for evaluating heterogeneity. If $P > 0.05$ or $I2 < 50\%$, the fixed effects model was used. If the result $P< 0.05$ or $I2 > 50\%$, the random effects model was used for analysis. The statistical significance level was set as $\alpha=0.05$, and $P < 0.05$ was considered statistically significant. As for publication bias of literature, Begg's test and Egger's test were used to detect it. If P values were both greater than 0.05, there was no publication bias. Otherwise, there is publication bias. To further assess the reliability of the included studies, sensitivity analyses were performed for endpoint events PFS, OS, and ORR to evaluate the robustness of the results and to identify possible sources of heterogeneity.

4. Results

4.1. Literature Screening

We searched PubMed, EMBASE, and Cochrane Library using the above retrieval methods, and reviewed the abstracts of ASCO and EMSO meetings. A lot of 457 related studies were preliminarily obtained, and 262 studies were still preserved after Endnote excluded duplicate papers. After carefully reading the title and abstract of the literature and excluding reviews, case reports and systematic reviews, 56 literatures were selected. Then, 49 studies that were inconsistent with the inclusion criteria and duplicate data were removed after a detailed reading of the full text. Finally, 7 studies were left, all of which were studies on the treatment of ICIs compared with sorafenib in first-line treatment of advanced HCC. A total of 4852 patients were included in the study, and the specific screening process was shown in the following figure (Figure 2).

4.2. Basic Characteristics and Statistics of the Included Studies

Seven RCTs were included in this review, all of which were stage II or III RCTs with ICIs-containing therapy compared with sorafenib in the first-line treatment of advanced HCC. Immune monotherapy was reported in CheckMate 459 and RATIONALE-301. ORIENT-32, SHR-1310-III-310, IMbrave150, and COSMIC-312 studies reported immune combination targeted therapy. And the HIMALAYA study reported immune monotherapy and dual ICIs therapy. The basic characteristics of the literature are shown in the table below (Table 1).

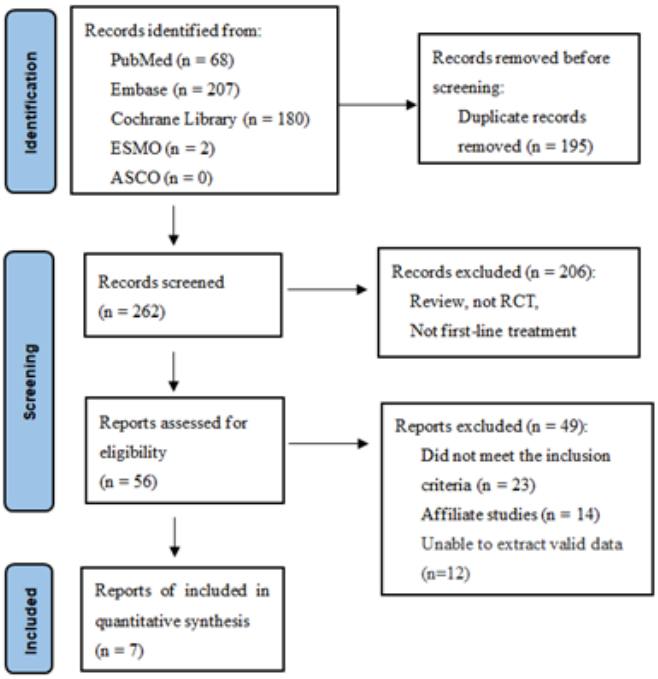

Figure 2: Screening Process of study selection and Inclusion.

Table 1: Basic characteristics of literature

		No.		Therapy		OS			PFS			ORR, %		3/4 TRAEs, %	
						Median, mo			Median, mo						
Study	Phase	EG	CG	EG	CG	EG	CG	HR(95%CI)	EG	CG	HR(95%CI)	EG	CG	EG	CG
CheckMate 459[15]	III	371	372	Nivolumab	Sorafenib	16.4	14.7	0.85(0.71-1.03)	3.7	3.8	0.93(0.79-1.10)	15	7	22	49
RATIONALE-301[16]	III	342	332	Tislelizumab	Sorafenib	15.9	14.1	0.85(0.71-1.02)	2.2	3.6	1.10(0.92-1.33)	14	5	NR	NR
HIMALAYA[17]	III	389	389	Durvalumab	Sorafenib	16.6	13.8	0.86(0.73-1.03)	3.7	4.1	1.02(0.88-1.19)	17	5	13	37
ORIENT-32[18]	II-III	380	191	Sintilimab+ Bevacizumab biosimilar	Sorafenib	NR	10.4	0.57(0.43-0.75)	4.6	2.8	0.56(0.46-0.70)	21	4	34	36
SHR-1310-lll-310[19]	III	272	271	Camrelizumab + Rivoceranib	Sorafenib	22.1	15.2	0.62(0.49-0.80)	5.6	3.7	0.52(0.41-0.65)	25	6	NR	NR
IMbrave150[20]	III	329	156	Atezolizumab+ Bevacizumab	Sorafenib	19.2	13.4	0.66(0.52-0.85)	6.9	4.3	0.65(0.53-0.81)	30	11	43	46
COSMIC-312[21]	III	432	217	Atezolizumab+ Cabozantinib	Sorafenib	15.4	15.5	0.90(0.69-1.18)	6.8	4.2	0.63(0.44-0.91)	11	4	54	32
HIMALAYA	III	393	389	Tremelimumab + Durvalumab	Sorafenib	16.4	13.8	0.78(0.65-0.93)	3.8	4.1	0.86(0.73-1.03)	20	5	26	37

EG, experimental group; CG, control group; OS, overall survival; PFS, progression free survival; ORR, objective remission rate; TRAE, treatment-related adverse events; HR, hazard ratio; NR, not reported

4.3. Results of Meta-Analysis

4.3.1. Immune monotherapy: In the study of immune monotherapy versus sorafenib in advanced HCC (Figure 3), it can be seen from the figure that there was no significant heterogeneity in the results of PFS (I2=16.6%, P=0.301), OS (I2=0.0%, P=0.994) and ORR (I2=0.0%, P=0.474), so a fixed-effect model was used for date statistics. Among them, immune monotherapy did not affect patients' PFS (HR=0.99, 95% CI: 0.91-1.08, P =0.851), indicating immune monotherapy could not prolong patients' PFS. The results of OS and ORR of immune monotherapy were (HR=0.85, 95% CI: 0.77-0.94, P=0.002) and (OR=2.98, 95% CI: 2.20-4.02, P<0.001), respectively. It can be seen that compared with sorafenib in first-line treatment of advanced HCC, the immune monotherapy reduced the risk of death by 15 percent and improved the objective response rate by nearly three times.

4.3.2. Immune-based combination therapy: In the immune-based combination therapy group (Figure 3), the heterogeneity test result of PFS was (I2=81.3%, P<0.001), showing severe heterogeneity, so the random effects model is used. The results showed that combined immunotherapy prolonged PFS in patients with advanced

HCC compared with sorafenib (HR=0.65, 95% CI: 0.51-0.81, P<0.001), suggesting that combined immunotherapy could benefit PFS, delay tumor progression, and thus improve patients' quality of life. Heterogeneity test results of OS and ORR were divided into (I2 =49.8%, P < 0.093) and (I2 =0.0%, P<0.577), showing no obvious heterogeneity, therefore, the fixed-effect model was used for analysis. The results showed that combined immunotherapy could prolong OS (HR=0.71, 95% CI: 0.64-0.79, P<0.001), ORR (OR=4.38, 95% CI: 3.34-5.76, P<0.001). The results showed that combined immunotherapy improved OS and reduced the risk of death by 29% compared with sorafenib, moreover, the short-term efficacy of the patients was significantly improved, and the ORR was increased by 4.38 times.

4.4. Subgroup Analysis

To explore the heterogeneity among the included literature, an exploratory post-treatment subgroup analysis was conducted to explore the dominant population and clinical benefit indicators based on the clinicopathological characteristics of patients from the two levels of immune monotherapy and immune combination therapy (Figure 4).

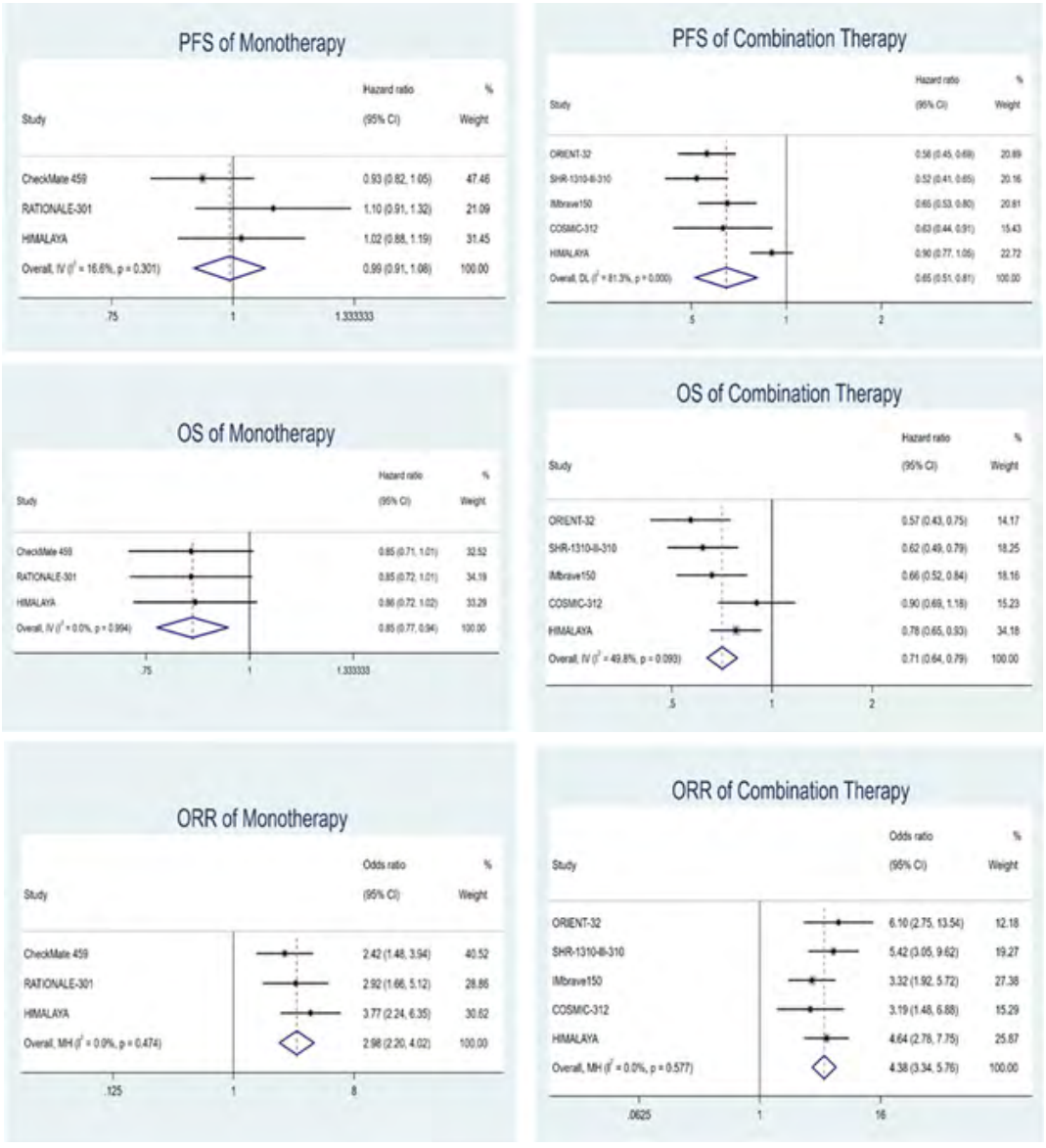

Figure 3: Survival analysis of immune monotherapy and immune-based combination therapy versus Sorafenib.
(a) HR of PFS with immune monotherapy. (b) HR of PFS with immune-based combination therapy. (c) HR of OS with immune monotherapy. (d) HR of OS with immune-based combination therapy. (e) OR of ORR with immune monotherapy. (f) OR of ORR with immune-based combination therapy. PFS, progression-free survival; OS, overall survival; ORR, objective response rate; HR, Hazard ratio; OR, Odds Ratio.

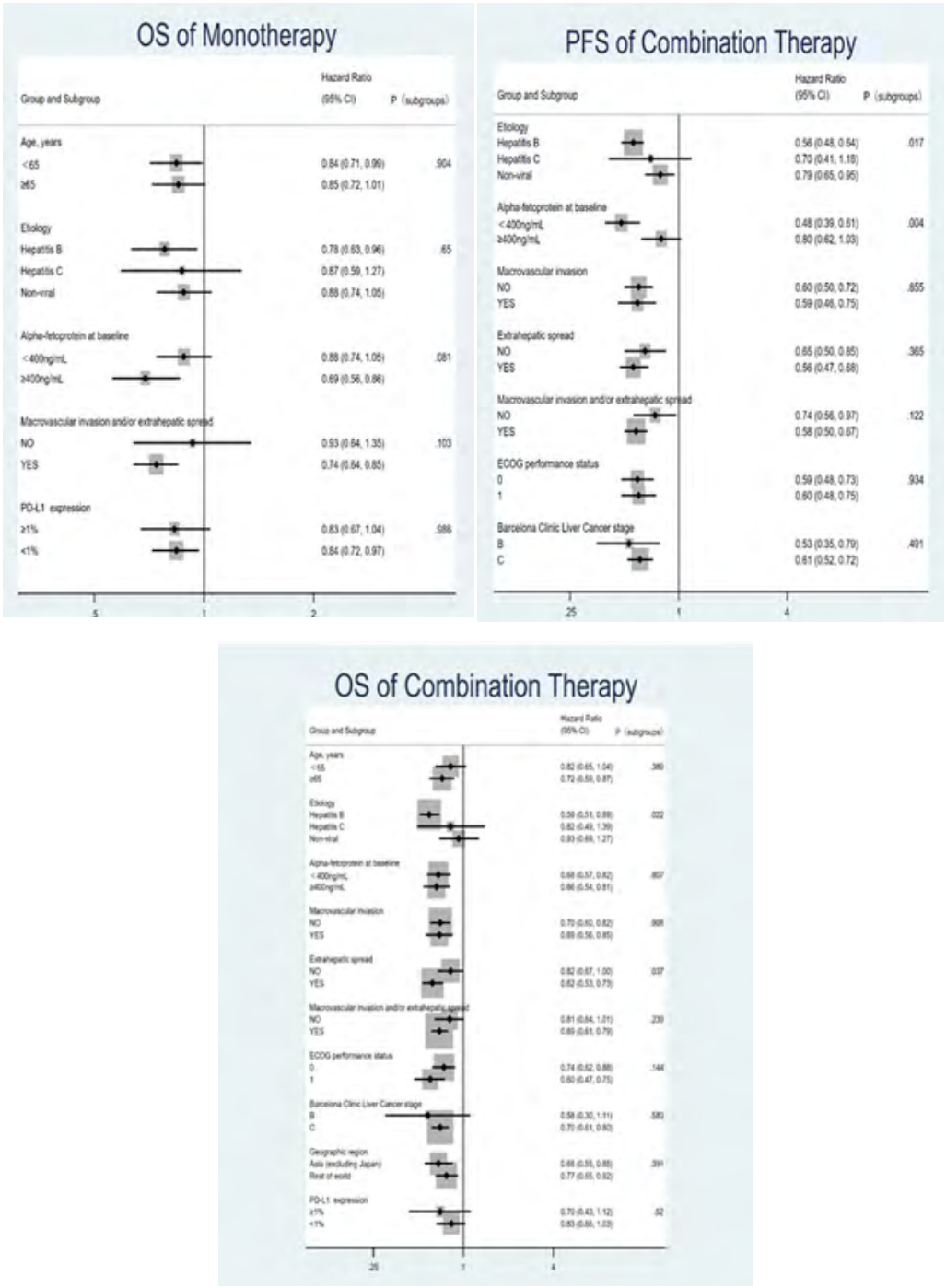

Figure 4: Subgroup analysis of immune monotherapy and immune-based combination therapy versus Sorafenib.
Subgroup analysis of OS(a) was performed based on clinicopathological features of immune monotherapy. Subgroup analysis of PFS (b) and OS (c) was performed based on clinicopathological features of Immune-based combination therapy.
PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1

4.4.1. Immune monotherapy: Two articles presented subgroup data on OS in patients with immune monotherapy versus sorafenib. From the data that can be extracted from the article and supplementary materials, the results of each subgroup were made, the survival analysis results and heterogeneity test results of the subgroups were summarized, and the summary table of OS subgroup analysis was obtained. As can be seen from the table, the benefit of OS in patients treated with immune monotherapy was independent of age (P=0.904), HBV infection (P=0.65), alpha-fetoprotein (AFP) level (P=0.081), macrovascular invasion(MVI) and/or extrahepatic metastasis(EHS) (P=0.103), and PD-L1 expression (P=0.986).

4.4.2. Immune-based combination therapy: Four articles presented subgroup data on OS and PFS in patients with combination immunotherapy versus Sorafenib. According to the above method, the OS and PFS subgroup analysis summary table is made respectively. The PFS results showed that the benefit of PFS in patients

was related to the etiology (HBV HR=0.56 vs HCV HR=0.70 vs non-viral HR=0.79, P=0.017) and APF levels (AFP<400ng/mL HR=0.48 vs AFP≥400ng/mL HR=0.80, P=0.004). Patients with HBV infection and AFP<400ng/mL had longer PFS. However, the benefit of PFS was not associated with MVI (P=0.855), EHS (P=0.365), MVI and/or EHS (P=0.122), Eastern Cooperative Oncology Group(ECOG) score (P=0.934), or Barcelona Clinic Liver Cancer (BCLC) (P=0.491). The OS results showed that the benefit of OS in patients was related to the etiology (HBV HR=0.59 vs HCV HR=0.82 vs non-viral HR=0.93, P=0.022) and EHS (no HR=0.82 vs. yes HR=0.62, P=0.037). Patients with HBV infection and EHS are more likely to profit from immune-based combination therapy and have longer survival. The overall survival benefit was not associated with age (P=0.389), AFP level (P=0.807), MVI (P=0.908), MVI and/or EHS (P=0.239), ECOG score (P=0.144), BCLC stage (P=0.583), ethnicity (P = 0.391), and PD-L1 expression (P =0.52).

4.5. Security Analysis

4.5.1. Immune monotherapy: Two studies reported the incidence of TRAEs, grade 3-4 TRAEs, and TRSAEs with immune monotherapy versus sorafenib (Figure 5). TRAEs (OR=0.19, 95% CI: 0.14-0.25, P<0.001), Grade 3-4 TRAEs (OR=0.27, 95% CI: 0.21-0.35, P<0.001), and TRSAEs (OR=0.99, 95% CI: 0.71-1.39, P = 0.953) showed that the incidence of TRAEs and Grade 3-4 TRAEs in first-line treatment of advanced HCC was significantly lower. That is, immune monotherapy can improve OS and ORR of patients, and also bring better safety for patients. The incidence of rash (OR=0.67, P=0.017), alopecia (OR=0.04, P<0.001), fatigue (OR=0.10, P=0.043), hypertension (OR=0.04, P<0.001), and metacarpal and toe erythema combined disorder (OR=0.01, P<0.001) were significantly reduced, however, the incidence of pruritus (OR=1.47, P=0.017) was increased.

4.5.2. Immune-based combination therapy: Four studies reported the incidence of TRAEs, grade 3-4 TRAEs, and TRSAEs in immune-based combination therapy versus sorafenib (Figure 5). The results of the immune combined treatment group were as follows: TRAEs (OR=0.64, 95% CI: 0.37-1.12, P=0.126), Grade 3-4 TRAEs (OR=1.04, 95% CI: 0.57-1.90, P=0.889) and TRSAEs (OR=1.98, 95% CI: 1.54-2.54, P<0.001). Among all TRAEs, statistically significant results were as follows: increased incidence of albuminuria (OR=3.24, P<0.001), elevated aspartate aminotransferase(AST) (OR=1.90, P=0.002), but significantly reduced incidence of diarrhea (OR=0.29, P<0.001), and metacarpophalangeal erythema complex disorder (OR=0.02, P<0.001). Overall data showed that immune-based combination therapy did not increase the incidence of TRAEs and grade 3-4 TRAEs while improving PFS, OS, and ORR in patients, but increased the incidence of elevated TRSAE, albuminuria, and AST.

4.6. Sensitivity Analysis

We performed sensitivity analyses for the primary endpoint events PFS, OS, and ORR of immune monotherapy and immune-based combination therapy, to further evaluate the robustness of the results. Among the included studies, the results of each combined effect size did not change significantly after the deletion of any study, which did not affect our conclusions. These results indicated that the sensitivity of PFS, OS, and ORR was low in immune monotherapy and immune-based combination therapy, and the results were robust and reliable (Figure 6).

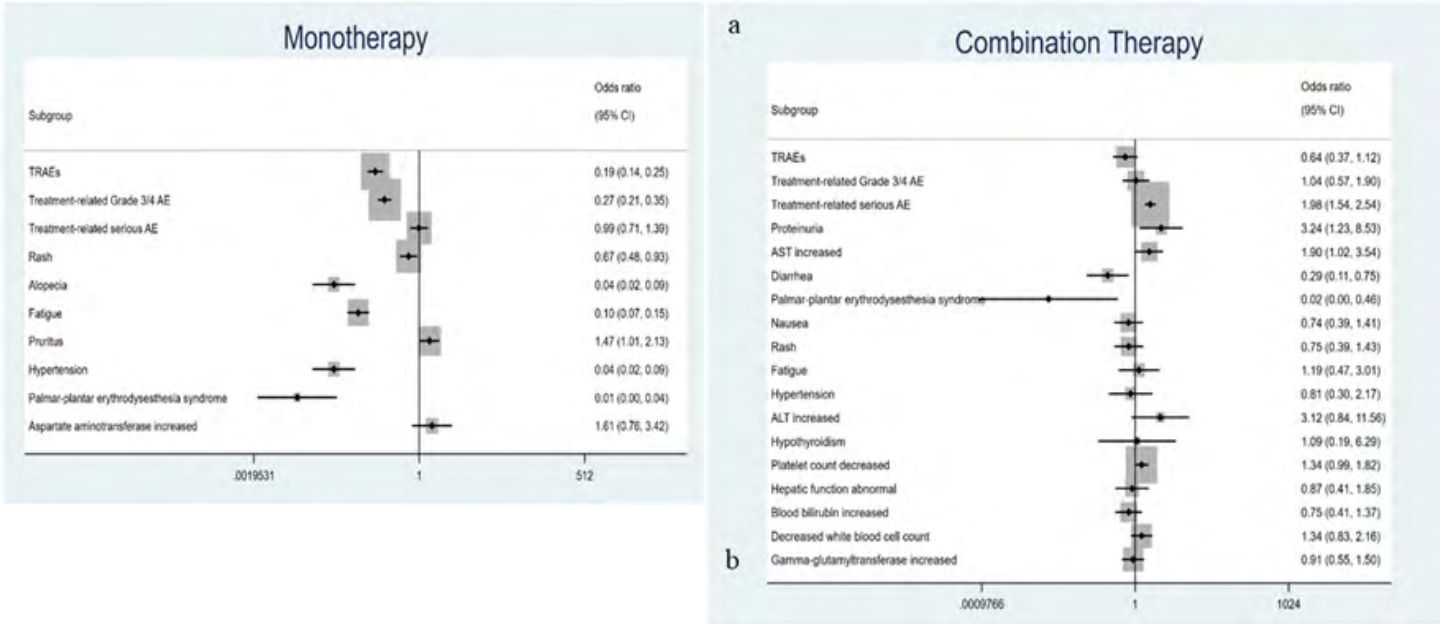

Figure 5: Safety analysis of immune monotherapy and immune-based combination therapy versus Sorafenib.
(a) Safety analysis of immune monotherapy. (b) Safety analysis of immune monotherapy
TRAEs, Treatment-related adverse events; AE, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

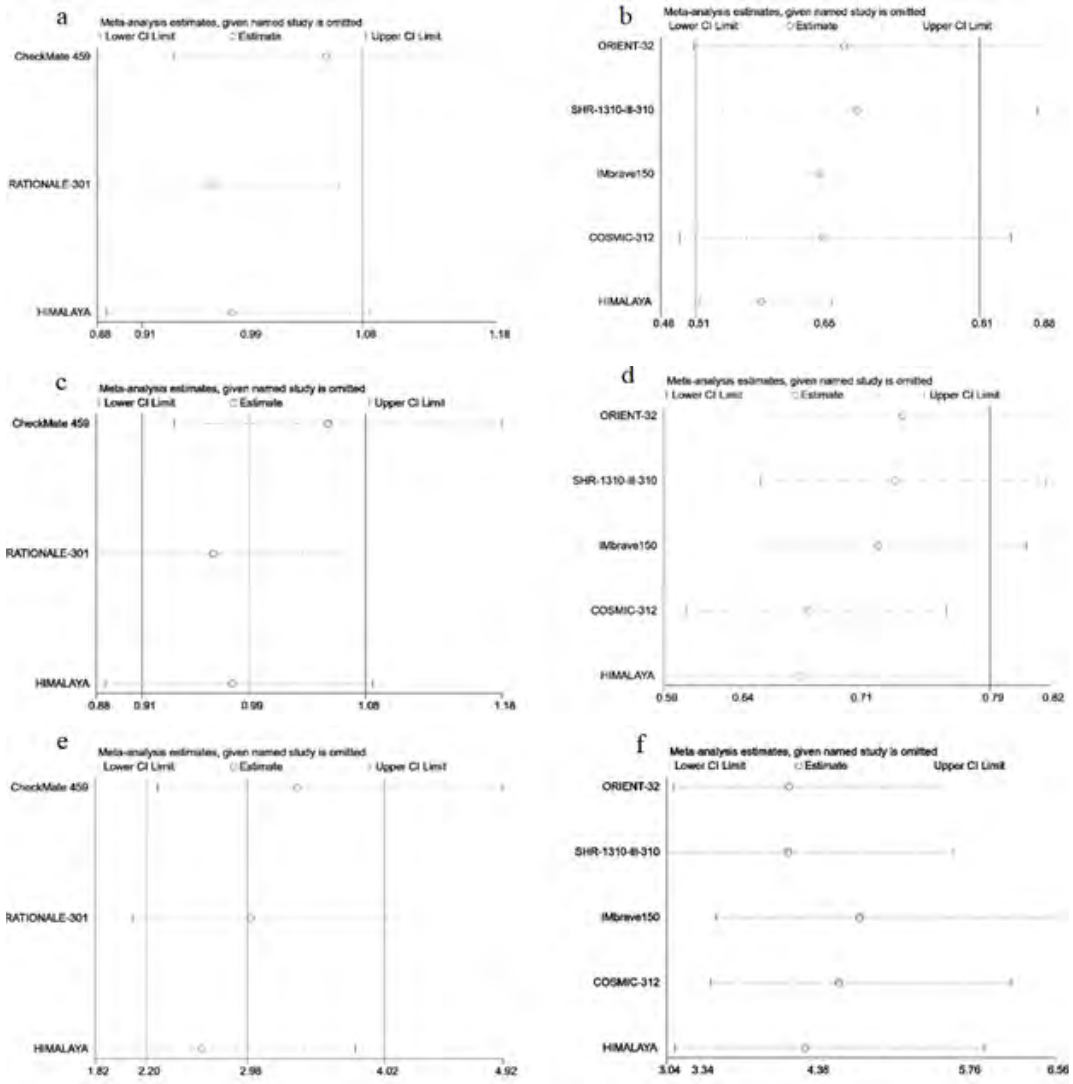

Figure 6: Sensitivity analysis of immune monotherapy and immune-based combination therapy versus Sorafenib.
(a) PFS of immune monotherapy. (b) PFS of immune-based combination therapy. (c) OS of immune monotherapy. (d) OS of immune-based combination therapy. (e) ORR of immune monotherapy. (f) ORR of immune-based combination therapy. PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

4.7. Publication Bias

The publication deviations of immune monotherapy were ORR(Begg's test, P=0.296; Egger's test, P=0.068), OS (Begg's test, P=1.0; Egger's test, P=0.967) and ORR (Begg's test, P=1.0; Egger's test, P=0.739); the publication deviations of immune-based combination therapy were PFS (Begg's test, P=0.806; Egger's test, P=0.250), OS (Begg's test, P=0.806; Egger's test, P=0.509) and ORR (Begg's test, P=0.806; Egger's test, P=0.891). In the results of the study of immune monotherapy and immune-based combination therapy, the P value of both tests was >0.05, indicating that there was no significant publication bias in our meta-analysis.

5. Discussion

At present, the global burden of liver cancer is large, the incidence is on the rise, the mortality rate is high and the prognosis is poor. HCC is the main pathological type of liver cancer, due to the lack of early symptoms, most of them are advanced when they are found, and the treatment effect of advanced HCC is generally poor, and the prognosis is not good, so new treatment methods are needed to improve prolong the survival of patients with advanced HCC. With the development of molecular biology and tumor biology, various new tumor immunotherapy has emerged as the times require, which has become another effective means for the clinical treatment of tumors. At present, tumor immunotherapy drugs are gradually widely used in lung cancer [22], gastroesophageal and colorectal cancer [23], and trials involving ICIs have also shown some success in advanced HCC, breaking the dominance of tyrosine kinase inhibitors (TKIs) in first-line treatment of advanced hepatocellular carcinoma. However, while we focus on the benefits of ICIs, we should also be mindful of their limitations, including the high cost, high risk, and the limited number of people who benefit from these treatments. Therefore we conducted this meta-analysis to evaluate the efficacy and safety of ICIs-containing therapy versus sorafenib in first-line therapy of advanced HCC by

systematically meta-analysis of data from the published literature, looking for dominant populations and indicators of clinical benefit.

At present, two meta-analyses on ICIs' first-line treatment of advanced HCC have been published [24, 25]. Different from these two meta-analyses, our study obtained relevant data from the latest domestic and foreign studies and separately studied the efficacy and safety of immune monotherapy and immune combined therapy. To further explore the clinical benefit population and reliable biomarkers, a subgroup analysis of outcome indicators PFS and OS was conducted.

Seven RCTs totaling 4852 patients (2915 treated with immune checkpoint inhibitors and 1937 treated with sorafenib) were included in this review. Our findings suggest that in the first-line treatment of advanced HCC, immune monotherapy can prolong the patient's OS and increase the patient's ORR, although it does not prolong the patient's PFS. Immune-based combination therapy can benefit both PFS and OS and significantly increase ORR, this is consistent with the findings of Rizzo, Alessandro et al [25]. Therefore, the efficacy of ICIs in the first-line treatment of advanced HCC is undoubted, and the main challenge is the discovery and validation of dominant populations and predictive biomarkers.

To further explore the potential sources of heterogeneity, as well as the clinically beneficial population and reliable biomarkers, we performed subgroup analyses of PFS and OS for immune monotherapy and immune combination therapy for the extractable data in the article and supplementary materials. According to the results of the analysis, it can be seen that in the immune monotherapy group, the benefit of OS was independent of age (P=0.904) and HBV infection (P=0.65), AFP level (P=0.081), MSI and/or EHS (P=0.103), and PD-L1 expression (P=0.986). In combination therapy, HBV infection with PFS (HBV: HR=0.56 vs HCV: HR=0.70 vs Non-viral: HR=0.79, P=0.017) and OS(HBV: HR=0.59 vs HCV: HR=0.82 vs Non-viral: HR= 0.93, P=0.022) had better efficacy, significantly improving both PFS and OS, reducing the risk of disease progression by 44 percent and the risk of death by 41 percent. The TME of HCC may be altered under chronic inflammatory stimulation caused by long-term HBV infection, resulting in the formation of a peripheral immunosuppressive microenvironment, thereby impairing immune surveillance [26, 27]. Moreover, the SHARP and AP study showed that the benefit was greater in patients with HCV infection who received sorafenib compared with placebo [28]. We also found that patients with AFP<400 ng/mL benefited better from PFS in the immune combination therapy group (AFP<400 ng/ mL HR=0.48 vs AFP≥400ng/mL HR=0.80, P=0.004), reducing the patient's risk of disease progression by 52%. This may be related to the effect of AFP level on the prognosis of the disease itself, with patients with AFP ≥ 400 ng/ml having a poor prognosis[29]. HCC patients with AFP≥400ng/ml may influence the prognosis by promoting DNA methylation of overexpressed promoters in tumor tissues, thus driving tumor tissue overexpression, for another, may be related to the activation of the tumor VEGF pathway, and ramucirumab can benefit the survival of patients with an AFP≥400 ng/ml [30-32]. In addition, there are reports on the correlation between AFP levels and OS and PFS in HCC patients treated with ICIs, indicating that high AFP levels increase the risk of disease progression and death in patients[[33]. At the same time, the AFP response is also a predictor of ORR, PFS, and OS, in the early days after ICIs treatment, patients with reduced AFP levels have better outcomes [34]. In addition, we found that the benefit of OS was more pronounced in patients with EHS (no HR=0.82 vs yes HR=0.62, P=0.037), However, the meta-analysis has shown that EHS does not affect the benefit of OS in HCC patients treated with ICIs [35], which may require more evidence to clarify whether EHS is a prognostic factor for advanced HCC immunotherapy.

Although immunotherapy plays an important role in the field of tumor treatment, there are still 50%-80% of tumor patients who do not benefit from immunotherapy, mainly because some patients cannot tolerate serious adverse reactions during treatment [11]. The results of our study showed that compared with sorafenib, immune monotherapy can significantly reduce the incidence of TRAEs and grade 3-4 TRAEs, and there is no significant difference in the incidence of TRSAEs. This indicates that the safety of immune monotherapy is controllable. Immune-based combination therapy benefits patients without increasing the incidence of TRAEs and grade 3-4 TRAEs, but increases TRSAE, proteinuria, and AST increased incidence, so we should attach importance to the management of adverse events in clinical practice.

In addition, to evaluate the robustness of the results, sensitivity analysis was also performed for the outcome indicators PFS, OS, and ORR of immune monotherapy and immune-based combination therapy. The deletion of any of the studies did not affect the combined statistics of PFS, OS, and ORR, indicating that the literature may come from the same population. In other words, there is no obvious heterogeneity, indicating that the results are robust and reliable.

Our study also had some limitations. First, we collected only seven articles, failed to perform meta-regression to provide a basis for subsequent subgroup analyses, and performed post hoc exploratory subgroup analyses, which may have not accurately obtained predominance populations. Secondly, under the premise of only one set of data on dual ICIs combination therapy, this experiment failed to separately compare the differences in efficacy and safety between immune combination targeted therapy and dual immunotherapy. Furthermore, the subgroup analysis was not conducted according to PD-1 and PD-L1 inhibitors classification effectively, although they both act on the PD-1/PD-L1 pathway, they are expressed on different cell surfaces and different tumor microenvironments, so efficacy and safety may be different. Finally, patients with high PD-L1 expression are the dominant population

that benefits from immunotherapy, but in our study, the benefit of patients with advanced HCC treated with ICIs was not different due to the PD-L1 expression. This may require further clinical data to demonstrate.

However, when further exploring the differences in the efficacy of ICIs in the treatment of HCC of different etiologies, we found conflicting results. Among them, Zhu et al [36] found that there was no significant difference in therapeutic effect between viral and non-viral HCC patients who received ICIs treatment. Pfister et al [37] compared with viral HCC, non-viral HCC patients, especially NASH-HCC patients, had less effectiveness in ICIs treatment. However, Murai et al [38] found that the TME characteristics of steatosis HCC are immune depletion and high expression of PD-L1, steatosis HCC patients treated with PD-L1 inhibitors combined with anti-VEGF showed significantly longer PFS than non-steatosis HCC patients, suggesting that intratumor steatosis may be a potential biomarker for predicting the efficacy of ICIs in advanced HCC. In summary, patients with HCC of different clinical etiologies may show different efficacy when treated with ICIs, therefore, more experiments are needed to look for advanced HCC effective clinical predictors of immunotherapy.

Based on the above contradictory results of NASH-related HCC response to ICIs, and NASH associated with metabolic syndrome or diabetes has gradually become one of the main causes of the rapid growth of HCC [3], NASH/non-alcoholic fatty liver disease (NAFLD) may be considered as an independent stratification factor in the etiology of HCC in large clinical trials. In addition, co-inhibitory receptors lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin domain and mucin domain-3 (TIM-3), and T cell immune receptor with Ig and ITIM domains (TIGIT) play a role in immune evasion by regulating T cell function [39], targeting TIM-3, TIGIT monotherapy or in combination with PD-1/PD-L1, CTLA-4 inhibitors, in various cancer types trials are ongoing, and their studies in HCC need to be progressively carried out [40]. Although we have seen that these therapies have significantly improved patient survival and more and more patients have achieved durable responses, there has been no significant increase in adverse effects. For another, there are still some patients with poor treatment effects, who can't prolong their survival, or improve their quality of life. Therefore, new drugs are needed in the future to achieve more precise and individualized treatment, such as adoptive cell therapy, neoantigen vaccine, immunostimulatory monoclonal antibody, bispecific antibody, and so on [41].

All in all, the data from our meta-analysis showed that, although immune monotherapy could not improve patients' PFS, it could improve patients' ORR and prolong patients' OS under the premise of providing good safety for patients. In the immune-based combination therapy group, patients' PFS and OS were prolonged to varying degrees, and patients' ORR was significantly improved, and the benefit was more pronounced in patients with HBV infection, AFP<400ng/mL, and EHS, but we should pay attention to the occurrence of TRSAEs, albuminuria, and elevated AST. So we should do a good job in the clinical detection of related adverse reactions. However, this is just our preliminary research result, which needs more clinical research and basic experiments to further explore and verify.

6. Conclusion

In the first-line treatment of advanced HCC, compared with sorafenib, immune monotherapy can benefit OS and ORR, and reduce the occurrence of TRAEs and grade 3-4 TRAEs. Immune-based combination therapy can significantly benefit PFS, OS, and ORR, and the benefit of PFS was more obvious in patients with HBV infection and AFP<400ng/ml, the benefit of OS was more obvious in patients with HBV infection and EHS, and overall adverse reactions were controllable, but we should pay attention to the incidence of TRSAEs, albuminuria, and elevated AST.

7. Statements and Declarations

7.1. Funding

This work was supported by the "521 Project" scientific research funding project of Lianyungang City (grant numbers LYG06521202157), the Science and Technology Bureau Key R&D Program (Social Development) Project of Lianyungang City (grant numbers SF2224).

7.2. Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

7.3. Author Contributions

Guanhong Huang, Xuzhu Gao, Yanan Chen, Qiulu Wang, and others decided on the topic. Yanan Chen and Yongliang Yang completed the search and screening of the article. Yanan Chen, Qiulu Wan, and Haotian Shang completed the production of charts and analysis of data. The first draft of the manuscript was written by Yanan Chen, and all authors contributed to the revision of the manuscript. All authors endorsed the submitted version.

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