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Comparing the clinical efficacy and safety of second-line targeted therapy and immunotherapy in patients with mid- to advanced stages of hepatocellular carcinoma – A systematic review and meta-analysis of randomized clinical trials

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Abstract. – OBJECTIVE: The aim of this study was to examine the efficacy and safety of second-line immunotherapy and targeted treatment in hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: From January 2000 to January 2023, ProQuest, PubMed, Web of Science, Scopus, Embase, and the Cochrane Library databases were searched for randomized controlled trials (RCTs) using immunotherapy or targeted therapy as second-line therapy for mid-to-advanced stages of HCC. Overall survival (OS), progression-free survival (PFS), and adverse events (AEs) are all examples of measures of success.

RESULTS: This analysis included twenty Randomized Clinical Trials (RCTs) from phases II and III. Collective data revealed better OS with immunotherapy (HR = 0.79; 95% CI: 0.67, 0.93 *vs*. 0.85; 95% CI: 0.78, 0.92), while the targeted therapy played a more effective role in PFS (0.67; 95% CI: 0.56, 0.81). Also, the second-line immunotherapy had a lower odds ratio of AEs of grades 3-5 than the targeted therapy did (OR = 1.75; 95% CI = 0.89, 3.46).

CONCLUSIONS: Overall, it appears that targeted medication and immunotherapy as a second-line treatment strategy have generally improved substantially, as well as progression-free survival for patients with mid-to-advanced HCC. Although it is difficult to judge their efficiency, the occurrences of AEs were greater in targeted therapy compared to immunotherapy.

Key Words:
Immunotherapy, Targeted therapy, Unresectable hepatocellular carcinoma, Second-line, Placebo.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most frequent cancer worldwide, which makes it one of the most important causes of mortality and a significant barrier to a long and healthy life[1]. In 2020[2], the number of new cases of liver cancer reached 905,677, and 8.3% of 9.9 million annual cancer fatalities were attributable to liver cancer in both sexes. According to a review of the medical literature[2,3], HCC accounts for more than 70% of primary liver cancer cases, with an expected 5-year overall survival (OS) rate of 2% and one-fifth of patients presenting with advanced disease. The late diagnosis of tumor aggregates has rendered primary local treatments such as surgical procedures, chemotherapy, radiotherapy, and trans-arterial chemoembolization (TACE), ineffective for the majority of patients with HCC[4]. With the advancement of biological sciences and the elucidation of the function of key molecules in the pathogenesis of liver tumor cells, scientists have turned their attention to more targeted, more effective, and systemic therapeutic strategies[5,6].

Immunotherapy and targeted therapy are among the most essential, and they have yielded promising results in multiple solid tumor clinical trials, including those for HCC[7]. Cancer immunotherapy refers to a collection of treatment methods that work with the body's immune system to inhibit tumor development and spread. The cornerstones of cancer immunotherapy include the administration of cytokines, the delivery of vaccines against cancer, the infecting of malignant cells with oncolytic viruses, the blocking of immunological checkpoints, and the selective transfer of tailored cells (T cells, natural killer cells, and macrophages)[8]. Immunotherapy has become an effective treatment for a variety of malignancies, including HCC, and individuals whose tumors have spread or are otherwise inoperable can

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use it as a first-line treatment[9]. Mechanistically, targeted therapy inhibits tumor growth and metastasis by binding to and disrupting the function of individual molecules. The high incidence of tumor recurrence and drug-related adverse effects pose challenges despite the satisfactory initial response to targeted therapy, which resulted in increased survival in certain HCC patients[10].

The United States Food and Drug Administration (US-FDA)[11] has gradually approved many immunotherapy and targeted therapy drugs for the first-line treatment of advanced or extra-hepatic HCC, such as atezolizumab with bevacizumab, sorafenib, and lenvatinib. The others, including cabozantinib, regorafenib, ramucirumab, pembrolizumab, nivolumab, and nivolumab plus ipilimumab, are approved for patients whose cancer progressed during first-line treatment. Despite this, the European Medicines Agency (EMA)[12,13] did not approve Pembrolizumab or Nivolumab monotherapy for the treatment of advanced HCC because neither drug significantly improved OS. In a multinational RCT on the effects of second-line enzalutamide monotherapy, Ryoo et al[14] demonstrated in 2021 that the use of this targeted treatment dampens the OS of patients with HCC and PFS by a hazard ratio (HR) of 1.15 and 1.06, respectively, compared to placebo. In addition, the administration of this therapy in this comparison enhanced the OR of AEs to 1.09. In contrast, Abou-Alfa et al[15] demonstrated in 2016 that the use of codrituzumab-targeted therapy enhances the OS and PFS in the same grade HCC patients against placebo group (HR = 0.96 and 0.0.97) and surprisingly reduced the AEs OR to 0.18. Furthermore, a systematic review and network meta-analysis[16] comparing the effectiveness of first-line systemic therapy regimens for unresectable HCC found that sintilimab-bevacizumab combination, atezolizumab-bevacizumab combo, and donafenib had superior os results compared to sorafenib. Also, compared to Sorafenib-related survival, Liu et al[17] found that OS and PFs may be significantly improved using sintilimab with a biosimilar of bevacizumab and camrelizumab plus rivoceranib. Another trial found that the combination of atezolizumab and bevacizumab was just as effective as sintilimab and a biosimilar version of bevacizumab[18]. So, given the heterogeneity in the efficacy and safety of immunotherapies and targeted therapies for HCC, the absence of such a study based on our knowledge, as well as the significance of immunotherapy and targeted therapy in the second-line treatment of HCC, the purpose of this systematic review and meta-analysis was to compare the OS and PFS HRs, and also the adverse events (AEs) of RCTs examining the immunotherapies or targeted therapies as a second-line monotherapy option for different stages of HCC against placebo control.

Materials and Methods

The Preferred Reporting Items for System Reviews and Meta-Analyses (PRISMA)[19] guidelines were used to perform and report this systematic review and meta-analysis. The protocol for this research was also submitted to the PROSPERO database with the identification number CRD42023427843.

Search Strategy

To this end, we looked through PubMed, Embase, the Cochrane Library, Web of Science, Scopus, and the ProQuest electronic databases for articles published between January 2000 and January 2023. The search terms and their MESH (Medical Subject Headings) used to define the therapies were "hepatocellular carcinoma", "Immunotherapy", "Targeted therapy", and their synonyms. Our search procedure had English language preferences. Manually searching the reference lists of linked clinical trials and prior reviews yielded the identification of additional pertinent studies. The selection of articles was made based on the review of titles and abstracts, and then reading the full texts independently by two authors (Y.F. and H.Z.). In the event of disagreement between the two authors, a third author (J.L.) was brought into the conversation until a consensus was reached.

Inclusion and Exclusion Criteria

The PICO principles[20] served as the basis for the development of the inclusion/exclusion criteria used in this investigation.

Types of Articles

We emphasized RCT studies and other types of papers such as letters, case reports, case-control studies, types of conferences, reviews, and those without access to raw data were excluded. In addition, no experiments on animals or *in vitro* and *in silico* conditions were be considered. Only studies with the most recent and comprehensive data were kept when they originated from various stages of the same experiment.

Study Population

The study population had to meet all of the following characteristics: i) HCC patients had to show various Child-Pugh scores (A and B); ii) all entrants had to be above the age of 18; iii) the administration of second-line monotherapy of immunotherapy or targeted treatment in the experimental group against placebo control, rather than locoregional therapy, should be the primary focus of published works; iv) no restrictions based on age, height, weight, sexual orientation, or previous first-line therapy; v) the only difference between the intervention of the experimental and placebo control groups had to be in receiving second-line immunotherapy or targeted therapy.

Interventions and Comparator

Immunotherapy or targeted therapy were administered alone or in conjunction with other anticancer medications. The comparison group consisted of the underlying condition and/or all categories of one of the two treatment groups.

Outcomes

The primary outcomes included the measuring of OS (the period of time from a person's random selection to their death from any reason) and PFS [the interval between random assignment and the earliest occurrence of progressive disease as measured by RECIST version 1.1 (available at https://recist.eortc.org/recist-1-1-2/) or death from any cause] and the secondary outcomes were AEs related to therapy.

Data Extraction and Definitions

Each step of the process – identifying relevant studies, selecting them, extracting their data, and evaluating their potential for bias – was handled separately by two authors (H.M. and G.Y.). The authors addressed any points of contention. If two authors were unable to come to an agreement, a third author (Y.T.) was called to make a decision The data information were entered into an Excel spreadsheet. Article titles, primary authors, publication years, trial phases, research designs, applicable drugs and comparators, combination therapies, sample sizes, OS rates, PFS rates, grade 3-5 treatment-related adverse events (TRAEs), follow-up time, patient's baseline level, and national clinical trial identification numbers were collected from each study that met the inclusion criteria. Median, standard error (SE), changes in HR of OS, PFS, and the number of persons with TRAEs post-intervention were the outcomes.

Evaluation of Quality

Each study's risk of bias was evaluated using the Cochrane Collaboration's methodology for randomized trials, which takes into account the following areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. Review Manager (Version 5.1, Nordic Cochrane Centre, Cochrane, Copenhagen, Denmark) assessed the potential for bias.

Statistical Analysis

We utilized STATA software 14.0 (STATA Corp., University of Texas Station, Texas, USA), Excel 2019 (Excel, Microsoft Corp., USA), and Review Manager (RevMan, V.5.1, Nordic Cochrane Centre, Cochrane, Copenhagen, Denmark). For PFS and OS, we determined the combined hazard ratio (HR) and its 95% confidence interval (CI), and for grade ≥ 3 therapy-related AEs, we determined the pooled odds ratio (OR) and its 95% CI. The OR was calculated by the following formula; log(OR)=[log(UL-OR) +log(LL-OR)]/2; selog(OR)=[log(UL-OR)-log(LL-OR)]/ (1.96×2). To evaluate the model's level of heterogeneity, the I^2 was computed. We used the fixed effects model if we did not find any significant heterogeneity ($I^2 < 50\%$ or $p < 0.1$), and the random effects model otherwise. Both the funnel plot and the Egger test were used to look for evidence of publication bias. No publishing bias was shown to exist when the graph was symmetrical, but it was suggested when the graph was asymmetrical. If publication bias was suspected ($p < 0.05$), the "trim and fill" method developed by Duval and Tweedie was used to mitigate its effects on the analysis[21]. The cut-off for statistical significance was set at $p< 0.05$.

Results

Study Selection

At first, we uncovered 51,519 documents in electronic libraries and archives. When all the duplicates were removed, 32,763 remained. Following the screening of abstracts and titles, 20,500 items were omitted from further consideration. This number includes 5,128 reviews, 595 animal-focused studies, 733 papers written in a language other than English, 4,979 studies of other diseases, and 9,065 other articles excluded for various reasons such as conference types, case

reports/series, books, patents, theses, editorials, errata, short surveys, corrections, letters, notes, and so on. 12,263 papers were considered, but after the full-text screening, 12,243 were discarded because i) they did not provide relevant results, ii) did not successfully complete the clinical trial study, iii) did not successfully recruit patients, iv) did not present the final results of the research, v) focused on other types of liver disorders, vi) did not use a placebo in the control group, or vii) used combined treatment simultaneously with immunotherapy or targeted therapy. Twenty studies[12,14,15,22-38] with a total of 6,772 patients were included in the final meta-analysis. Figure 1 depicts the procedure for selecting relevant literature.

Study Characteristics

In addition, only 12 of the remaining 20 studies provided data on the total number of TRAEs in grades 3 through 5[12,14,15,22,23,25,26,31-33,35,38]. Nonetheless, each of the 20 studies included information on two main outcomes: OS and PFS. 75% of the studies was undertaken on a multinational sc ale[12,14,15,22-26,28,32-34,36-38], while the remaining studies[27,29-31,35] were conducted in multiple institutions in France[35], Japan[27,29], United Kingdom[30], and China[31]. In addition, these studies were conducted between 2010 and 2022. It should be noted that only two studies[12,38] used an immunotherapy drug (Pembrolizumab) for treatment, whereas the remaining 18 studies used targeted therapy drugs, such as Sunitinib[35], Codrituzumab[15], ADI-PEG 20[23], Regorafenib[25], Namodenoson[33], Tivantinib[27], Enzalutamide[14], Sorafenib[22,30], Axitinib[26], Ramucirumab[36,37], and Apatinib[31]. All studies included were randomized controlled trials of phase II and III designs, with patients who had completed their first line of treatment immediately preceding or immediately following the second line of treatment, with the only difference between the control group and the experimental group being the receipt of a placebo. The disease studied was hepatocellular carcinoma of moderate severity and advanced stage, as measured by Child Pogh scores A and B (Table I).

Publication Bias Test

Twenty studies were evaluated for publication bias. The funnel-shaped diagram reveals that the plurality of studies is located in the upper portion of the inverted funnel, while the distribution on the sides is even. In addition, the results of Egger's statistical test indicate that there is no publication bias in the included studies ($p = 0.834$ for HR of OS and $p = 0.899$ for HR of PFS). Also, the Cochrane tool's evaluation of the quality of the articles revealed that, in general, the studies were of high quality, and, with the exception of 8 studies, the greatest deficiency of the articles was the detection bias. Abou-Alfa et al[24] and Bruix et al[25] presented the highest-quality papers, while other included studies demonstrated the highest quality in the areas of selection bias and reporting bias, leaving only the study by Abou-Alfa et al[15] and Turpin et al[35] with an uncertain risk in these areas, respectively.

Major Outcomes: OS and PFS

OS cumulative statistics

Data on OS are available from 20 trials, including 18 with targeted therapeutic intervention[14,15,23-37,39] and two with immunotherapy[12,38]. Analyzing the HR findings, we found that both immunotherapies (HR = 0.79, 95% CI = 0.67, 0.93, $I^2 = 0\%$, $p = 0.005$) and targeted treatments (HR = 0.85, 95% CI = 0.79, 0.90, $I^2 = 27\%$, $p < 0.0001$) significantly improved OS. Statistical analysis showed that immunotherapy reduced mortality risk by 21% compared to targeted therapy's 15% reduction, but the overall effect was statistically significant when compared to placebo (HR = 0.84, 95% CI = 0.79, 0.89, $I^2 = 21\%$, $p < 0.0001$), and there was no heterogenicity between subgroups ($I^2 = 0\%$, $p = 0.43$) (Figure 2).

Progression-free survival (PFS) cumulative statistics

Figure 3 shows a forest plot depicting the combined results from all 20 studies that reported PFS information. Similar to the OS outcomes, the statistical analysis of PFS data showed an improvement in PFS for both intervention groups; however, the increase in PFS from targeted therapy intervention (HR = 0.67, 95% CI = 0.56, 0.81, $I^2 = 88\%$, $p < 0.0001$) was superior to immunotherapy (HR = 0.75, 95% CI = 0.64, 0.88, $I^2 = 0\%$, $p = 0.0005$). Both therapies enhanced PFS overall, although the latter was linked with a lower HR (HR = 0.67, 95% CI = 0.58, 0.80, $I^2 = 87\%$, $p < 0.00001$). In spite of this, no significant heterogeneity was found across the various groups ($I^2 = 0\%$, $p = 0.35$).

TRAE Cumulative Statistics

The data of TRAEs of grades 3-5 are shown in the forest plot in Figure 4. There was an increase in the OR of 1.75 (95% CI = 0.89, 3.46, I^2

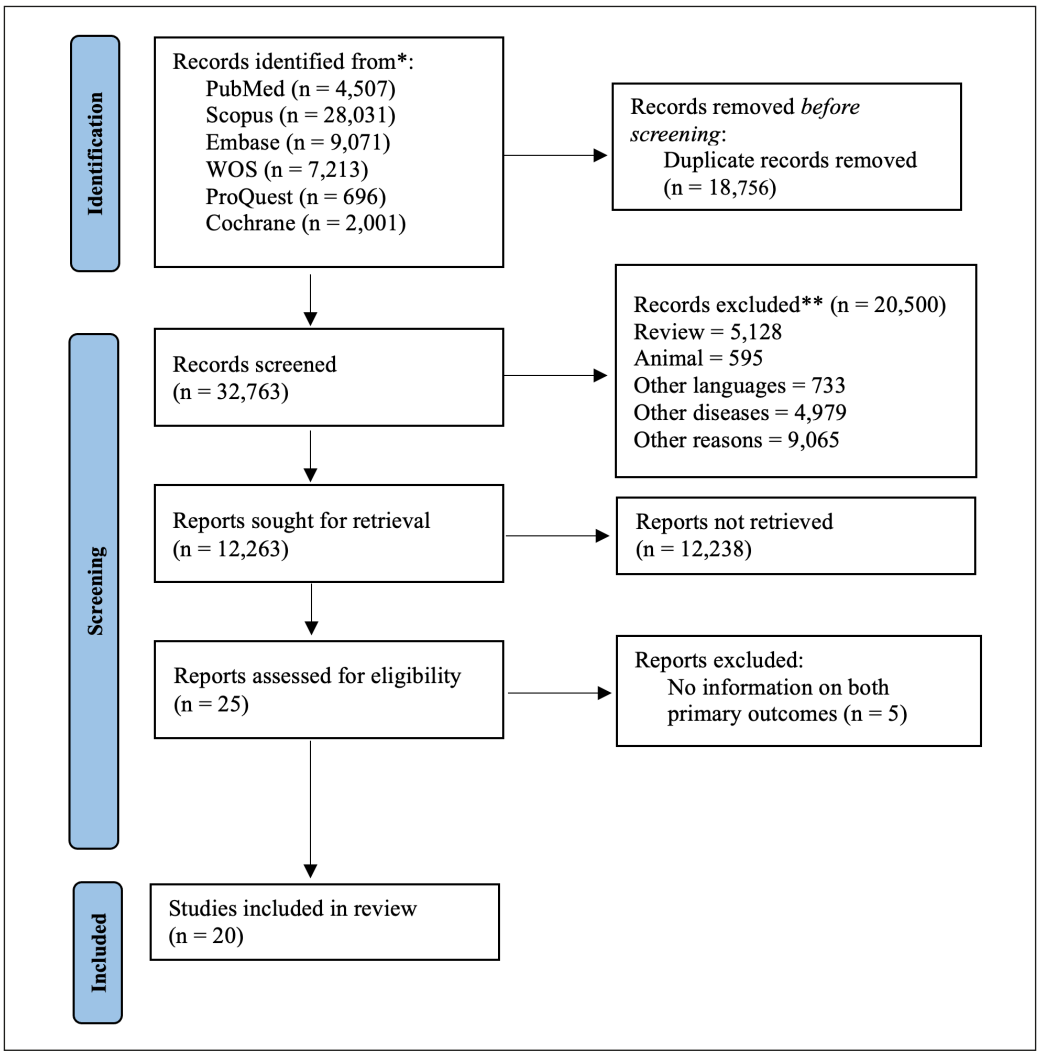

Figure 1. The screening and selection procedure as shown by the PRISMA flow diagram.

= 62%, $p = 0.10$) and 2.60 (95% CI = 1.37, 4.96, I^2 = 89%, $p = 0.004$) for HCC patients who received immunotherapy and targeted therapy interventions, respectively, according to the analysis of 12 studies[12,14,15,24-26,31-33,35,38,39]. The overall findings revealed that the OR for severe AEs in the treatment group was higher than in the placebo group after receiving immunotherapy or targeted therapy as a second-line treatment strategy (OR = 2.46, 95% CI = 1.41, 4.28, $I^2 = 89\%$, $p = 0.002$). However, there was no discernible heterogeneity difference between the two groups ($I^2 = 0\%$, $p = 0.41$).

Discussion

Twenty phase II and III RCT studies were included in this systematic review and meta-analysis to assess the effectiveness and safety of immunotherapy-based approaches *vs.* targeted therapeutic strategies as a second-line monotherapy option for patients with mid to advanced HCC. These findings suggested that patients with multiple stages of HCC might benefit from immunotherapy, as well as targeted therapy-based treatments, in terms of both OS and PFS. However, there are concerns about the safety of these two treatment approaches.

Generally, there are several options for second-line therapy of HCC patients, including the TKIs regorafenib and codrituzumab, as well as sunitinib, ADI-PEG 20, namodenoson, tivantinib, enzalutamide, sorafenib, axitinib, ramucirumab, and apatinib[3,14,15,22-37]. The FDA has approved[39] the monoclonal antibody ramucirumab for patients with an alpha-fetoprotein (AFP) level of at least 400 ng/mL. Currently, despite the failure of the

Table I. Main characteristics of the included studies.

Author/Year (Identifier)	Type of study/Phase	Type of therapy	Intervention		TRAEs (3-5)		Median age (Exp)	Median OS (m)	HR, 95% CI	Median PFS (m)	HR, 95% CI	Child-Pugh score
			Exp (n)	Ctrl (n)	Exp (n)	Ctrl (n)						
Finn et al[12]/2020 (NCT02702401)	RCT/III	IT	Pembrolizumab+BSC (278)	PL +BSC (135)	147	62	67	13.9	0.781	3	0.775	A/B
Turpin et al[35]/2020 (NCT01164202)	RCT/II, III	TT	TACE+sunitinib (39)	TACE+PL (39)	36	27	66	25	0.885	9.05	0.3868	A/B
Abou-Alfa et al[15]/2016 (NCT01507168)	RCT/II	TT	Codrituzumab (125)	PL (60)	114	59	64	8.7	0.96	2.6	0.97	A
Abou-Alfa et al[23]/2018 (NCT 01287585)	RCT/III	TT	ADI-PEG 20+BSC (424)	PL+BSC (211)	ND	ND	61	7.8	1.022	2.6	1.175	A/B
Bruix et al[25]/2017 (NCT01774344)	RCT/III	TT	Regorafenib+BSC (379)	PL+BSC (194)	202	41	64	10.6	0.63	3.1	0.46	A/B
Stemmer et al[33]/2021 (NCT02128958)	RCT/II	TT	Namodenoson (50)	PL (28)	1	1	62	4.1	0.82	2.5	0.86	B
Kudo et al[27]/2020 (NCT02029157)	RCT/III	TT	Tivantinib (134)	PL (61)	ND	ND	70	10.3	0.82	2.8	0.74	A/B
Ryoo et al[14]/2021 (NCT02528643)	RCT/II	TT	Enzalutamide (110)	PL (61)	13	6	64	7.8	1.15	2.2	1.04	A/B
Kudo et al[28]/2011 (NCT00494299)	RCT/III	TT	Sorafeni (229)	PL (229)	ND	ND	69	29.7	1.06	5.4	0.87	A/B
Kudo et al[29]/2017 (JapicCTI-090920)	RCT/III	TT	S-1 (223)	PL (111)	ND	ND	70	11.1	0.86	2.6	0.6	A/B
Abou-Alfa et al[24]/2018 (NCT01908426)	RCT/III	TT	Cabozantinib (470)	PL (237)	371	114	64	10.2	0.76	5.2	0.44	A
Meyer et al[30]/2017 (IS-RCTN93375053)	RCT/III	TT	TACE+Sorafenib (157)	TACE+PL (156)	ND	ND	65	21.03	0.91	7.93	0.99	A/B
Kang et al[26]/2015 (NCT01210495)	RCT/II	TT	axitinib+BSC (134)	PL+BSC (68)	109	26	61	12.7	0.907	3.6	0.618	A
Rimassa et al[32]/2018 (NCT01755767)	RCT/III	TT	Tivantinib (226)	PL (114)	125	63	66	8.4	0.97	2.1	0.96	A
Qin et al[31]/2021 (NCT02329860)	RCT/III	TT	Apatinib (261)	PL (132)	199	25	51	8.7	0.785	4.5	0.471	A/B
Santoro et al[34]/2013 (NCT00988741)	RCT/II	TT	Tivantinib (71)	PL (36)	ND	ND	70	6.6	0.9	1.5	0.64	A/B
Zhu et al[36]/2015 (NCT01140347)	RCT/III	TT	Ramucirumab (283)	PL (282)	ND	ND	64	9.2	0.87	2.8	0.63	A
Zhu et al[37]/2019 (NCT02435433)	RCT/III	TT	Ramucirumab (197)	PL (95)	ND	ND	64	8.5	0.71	2.8	0.452	A

RCT: randomized controlled trial, IT: Immunotherapy, TT: Targeted Therapy, Exp: Experimental, Ctrl: Control, BSC: Best Supportive Care, PL: Placebo, TACE: Transarterial Chemoembolization, Dox: doxorubicin, TRAEs (Treatment Related Adverse Events), OS: Overall survival, PFS: Progression-Free Survival, HR, Hazard Ratio, ND: Not-Determined.

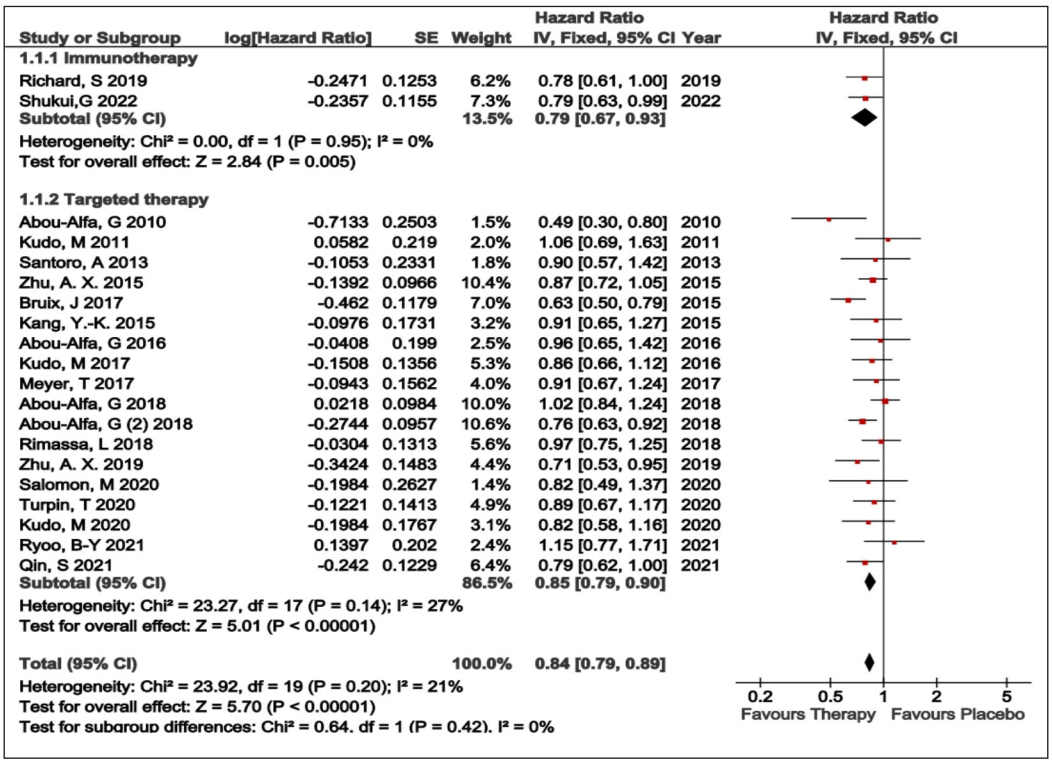

Figure 2. The hazard ratio of overall survival plotted in a forest using a Fixed-effects model for hepatocellular carcinoma.

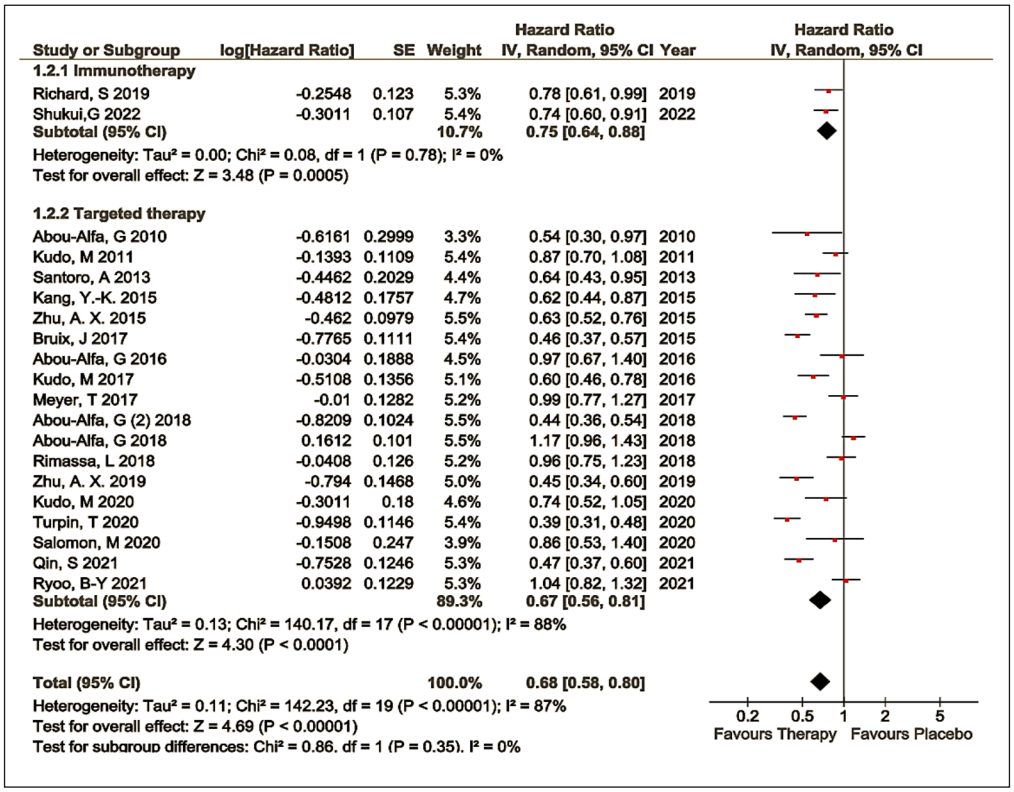

Figure 3. The hazard ratio of progression-free survival plotted in a forest using a random-effects model for hepatocellular carcinoma

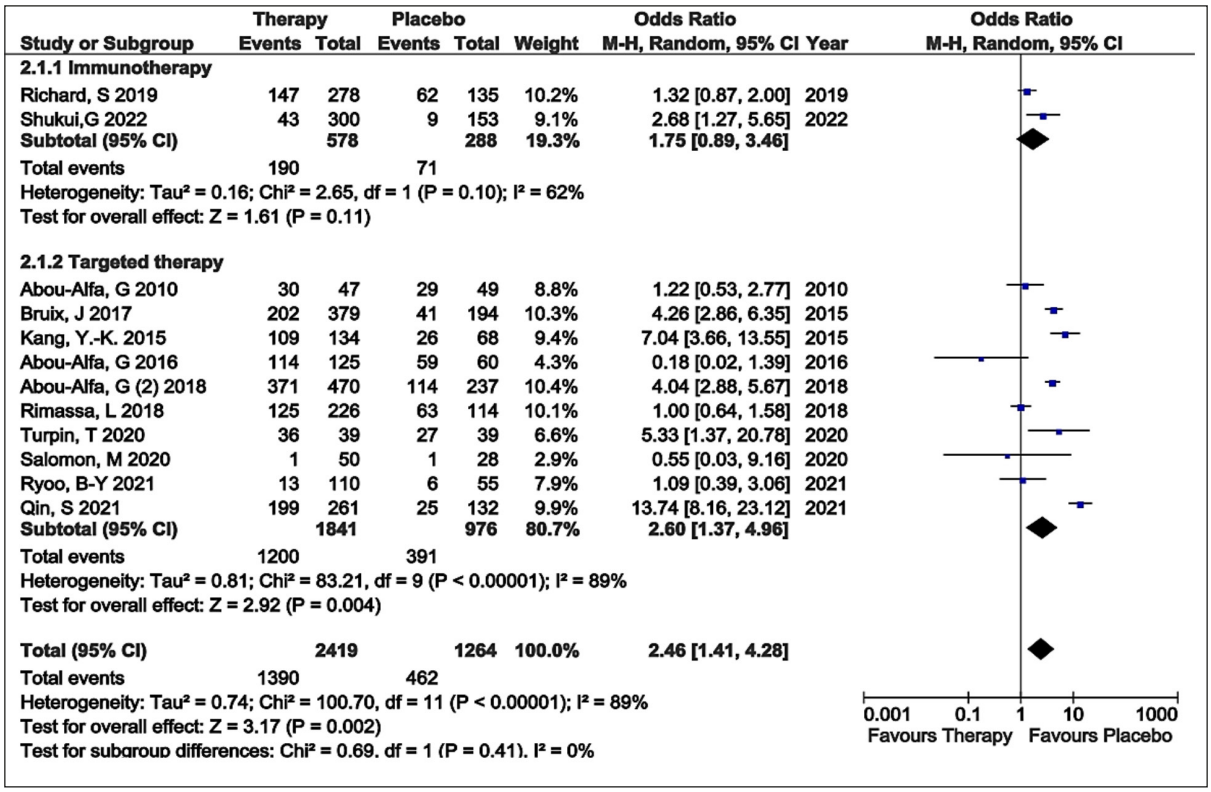

Figure 4. A forest plot of the odds ratios of treatment-related adverse events derived from a random-effects model of hepatocellular carcinoma.

phase III trial of second-line pembrolizumab, both nivolumab and pembrolizumab have been authorized[40] as single medicines based on phase II results. The combination of nivolumab, as a PD-1 blocker, and ipilimumab, as an anti-CTLA-4 monoclonal antibody, was recently authorized for use in second-line therapy[41]. Lenvatinib and sorafenib, as VEGFR inhibitors, are both single-agent alternatives in subsequent treatment according to the NCCN recommendations[42]; however, both drugs have not been investigated in the second line and do not have FDA approval in this scenario.

It is noteworthy to observe that in the clinical trial investigations under consideration, the clinical trial demographics varied when comparing second-line TKIs. For example, patients were only eligible for the regorafenib trial if they had previously tolerated a sorafenib dosage of at least 400 mg for about 72% of the preceding days of therapy cycle[43]. Moreover, the inclusion and exclusion criteria for the cabozantinib trial were more lenient than those of the other studies, allowing patients to enter even if they had not tolerated their first-line medication[24]. Patients with AFP levels of 400 ng/mL or greater were the only ones who benefited from treatment with ramucirumab[36,37]. The OS rates with regorafenib, cabozantinib, and ramucirumab were all rather close. Although comparing results from different studies is impossible, the HRs for the three different therapies were rather comparable. Although patients with an AFP level of 400 ng/mL or more tend to have a more aggressive illness that advances a bit quicker, this may explain why the HR for the ramucirumab trial was not as robust as that for the regorafenib or cabozantinib second-line therapy studies. The pembrolizumab had favorable response rates and improved OS and PFS in phase III trials. This suggests a therapeutic benefit for certain individuals with Child-Pugh scores A and B HCC, similar to that seen with a single-arm trial of nivolumab[11,44]. However, the immunotherapy was associated with several unpleasant side effects for which around half of the patients needed corticosteroids. Therefore, treatment risks and advantages must be thoroughly discussed with patients and their loved ones, and patients must be continuously followed. In relation to targeted therapies like regorafenib, cabozantinib, and ramucirumab, they are all quite comparable to one

another when it comes to their AEs and general safety. Ramucirumab, on the other hand, is administered intravenously and is not linked to the same frequency of diarrhea and hand-foot-and-skin responses[36,37] as regorafenib and cabozantinib[45]. Similarly, our analysis of relevant clinical studies yielded the same results. For example, in the treatment of Child-Pugh score A and B HCC patients, Finn et al[12] reported that the pembrolizumab therapy, an anti-PD-1 ICI, was associated with statistically significant and clinically meaningful improvement in both OS [13.9 month (m) *vs*. 10.6 m] and PFS (3 m *vs*. 2.8 m) compared to the placebo group. Also, in the targeted therapy side, clinically meaningful improvements in OS and PFS for mild to advanced HCC were reported with the combination of sorafenib (as a kinase inhibitor) plus TACE[30]. In another interesting study, the use of regorafenib, as a multi-kinase inhibitor, mediated a 37% reduction in the HR of death, which coincidentally decreased the HR of PFS[25]. However, the HR results of the OS and PFS of the enzalutamide and the OS HR of sorafenib therapy-based trials behaved in a manner that defied expectations and were slightly dissimilar[14]. Additionally, the combination of ADI-PEG 20, an arginine-degrading enzyme, with BSC (as per NCT 01287585) did not lower mortality risk in the HR analysis of the PFS. This outcome might contribute to the study's limitations in establishing the ideal dosage (18 mg/m^2) and treatment duration (10 weeks)[23]. Unfortunately, the findings regarding the efficacy of immunotherapy as a singular second-line treatment were extremely limited, with only two studies using an identified ICI[11,38].

Furthermore, our study confirms that this meta-analysis is not affected by publication bias, ensuring the reliability of its results. Lei et al[46] conducted a meta-analysis and network meta-analysis to evaluate the efficacy and safety of immune checkpoint inhibitors (ICIs) as primary therapy for HCC that cannot be surgically removed. Patients with unresectable HCC had better survival rates when treated with ICIs-based treatments, the researchers observed, with tolerable TRAEs. Although this review has produced some positive results, it may be difficult to interpret them in their entirety because of the low standard of study design and lack of integration among the research included. However, we observed that without a chain of etiological evidence, it is difficult to evaluate the success of ICI treatment for patients with varying conditions. RCTs and non-randomized RCTs, as well as cohort studies, were used in a recent systematic review and meta-analysis[47] assessing the effectiveness and safety of first-line targeted treatment and immunotherapy for patients with biliary tract cancer. According to the results, patients with unresectable biliary tract cancer may benefit from a higher objective response rate and longer lifetimes if they get a combination of immunotherapy and chemotherapy as first-line treatment. One of the significant complicating variables for examining the true impact of effective size was the inclusion of a variety of different types of clinical trials, including random and non-random trials and cohort studies, in this analysis. However, subgroup analysis for patients with various conditions is skewed due to the presence of the same issue, namely the unclear sequencing of critical information. Additionally, the effects of combination immunotherapy + targeted treatment *vs.* targeted therapy in inoperable patients with Child-Pugh score B HCC were evaluated in a systematic review and meta-analysis[48] of three RCTs. Based on the results of this research, it is clear that combination treatment has a higher potential to improve survival than single-targeted therapy does, although at the cost of more severe AEs.

Limitations

One significant limitation of the research is its reliance on data from only three RCTs. The risk of bias assessment points out that such a small sample size increases the likelihood of misleading results due to even minor variations in the studies. Additionally, the exclusive focus on patients with a score of B further exacerbates these methodological issues. To the best of our knowledge, no systematic reviews and meta-analyses have compared the efficacy and safety of immunotherapy treatment methods *vs.* targeted therapies as the second-line monotherapy for HCC patients so far. A few limited studies on patients with unresectable HCC have also been conducted, with meta-analyses[18,49-52] serving as the method of choice, and in associated systematic review and meta-analyses studies[47-50], combined treatments have been one of the comparisons arms[49].

Conclusions

Taken together, we observed that patients with mid-to-advanced HCC who received targeted/immunotherapy as a second-line monotherapy had significantly improved overall as well as progression-free survival than those who received a

placebo. This comparison was in the superiority of OS related to immunotherapy, while targeted therapy provided better survival without cancer progression. However, judgment in this area should be made with additional care given to the inadequate evidence of immunotherapy monotherapy research. Moreover, a greater rate of severe AEs (grades 3-5) was seen in the targeted treatment group than in immunotherapy, which should be considered in future studies.

Conflict of Interest
The authors declare that they have no conflict of interests.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

Data Availability
The data that support the findings of this study are available upon request from the corresponding author.

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None.

Authors' Contributions
JL, YF, HZ, HM, GY, and YT designed and supervised the study, performed the research, analyzed the data, wrote and revised the manuscript. All authors read and approved the final manuscript.

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