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Efficacy and safety of camrelizumab combined with TACE for hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Hepatocellular carcinoma (HCC) represents a highly lethal and recurrent neoplasm, with limited effective treatment regimens available. Camrelizumab, as a novel PD1 inhibitor combined with transcatheter arterial chemoembolization (TACE), has been widely used in the treatment of HCC. However, there remains a contentious debate regarding the clinical value of the TACE and camrelizumab combination. This study seeks to investigate the efficacy and safety of this combination treatment regimen in patients with HCC.

MATERIALS AND METHODS: The related studies were retrieved from four online databases, including PubMed, Cochrane Library, EMBASE, and Web of Science, up to June 1, 2023. The selection of studies was based on screening of titles, abstracts, and full-texts. The primary efficacy outcomes included complete response (CR), objective response rate (ORR), and disease control rate (DCR), while safety outcomes evaluated all treatment-related adverse events (AEs). Additionally, secondary outcomes such as overall (OS) and progression-free survival (PFS) were extracted for further survival analysis. The quality of the included trials was assessed using the MINORS tool. Publication bias was evaluated through funnel plot and Egger's test.

RESULTS: A total of 17 publications involving 1,377 cases were included. The pooled CR rate, ORR, and DCR of the patients treated with TACE plus camrelizumab had a pooled CR rate of 8% (95% CI: 0.01-0.15, p=0.03), ORR of 47% (95% CI: 0.42-0.52, p<0.00001) and DCR of 82% (95% CI: 0.77-0.88, p<0.00001), respectively. Compared with a control group that did not receive TACE or camrelizumab, the pooled RR of CR rate, ORR, and DCR were 1.61 (95% CI: 1.27-2.04, p<0.0001), 1.56 (95% CI: 1.19-2.05, p=0.001) and 1.55 (95% CI: 1.19-2.03, p=0.001), respectively. Besides, the combination regimen can prolong the OS (HR=2.60, 95% CI: 2.25-3.02, p<0.00001) and PFS (HR=4.90, 95% CI: 1.94-12.38, p=0.0008). However, the incidence of treatment-related AEs was relatively high (77%), with 29% for grade 3 AEs. The most common AEs observed were pain (47%), fever (46%), hepatic function abnormalities (44%), hypoalbuminemia (39%), and hypertension (37%). The combination treatment did not increase the incidence of AEs compared to the control group, except for the hand-foot skin reaction (RR=0.85, 0.74-0.97, p=0.01), hepatic encephalopathy (RR=4.29, 2.51-7.35, p<0.00001) and nausea (RR=1.35, 1.13-1.61, p=0.001).

CONCLUSIONS: Combination therapy of TACE plus camrelizumab has shown notable clinical benefits, improved survival, and a manageable safety profile in patients with HCC, but it is essential to monitor and manage the specific toxicities, especially for the camrelizumab-related AEs.

Key Words:
Hepatocellular carcinoma, Camrelizumab, TACE, Efficacy, Safety.

Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the third leading cause of cancer-related deaths worldwide, with a 5-year survival rate of 18%[1]. Although surgical resection is the primary treatment for HCC, it is plagued by a high rate of postoperative recurrence. Additionally, unresectable and recurrent HCC is

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somewhat resistant to treatment modalities such as radiotherapy, chemotherapy, immunotherapy, and target therapy. Multimodality combination treatments have emerged as a promising approach to managing HCC, becoming a routine treatment trend[2,3]. However, it is still uncertain which combination regimen can truly maximize the benefits for HCC patients.

Transcatheter arterial chemoembolization (TACE) is a common interventional treatment for HCC. It involves delivering a concentrated dose of chemotherapy directly to the tumor site, significantly reducing the toxicity to normal tissues. Moreover, TACE can induce tumor ischemic and necrosis by blocking the blood supply to the tumor[4]. Many clinical trials[5,6] have demonstrated that TACE can improve the disease response rate and significantly prolong the survival time of HCC patients compared to conventional chemotherapy. However, some patients may not be responsive to TACE due to individual differences. Additionally, TACE is a localized treatment method and may have limited efficacy in preventing distant metastasis[7]. Besides, the 2-year OS of 64.6% and the 13.5-month progression-free survival (PFS) achieved with TACE alone are not entirely satisfactory. However, it has been reported that TACE can activate the body's immune response, leading to an increased immune attack against the tumor[5]. Therefore, combining TACE with immune checkpoint inhibitors may potentially enhance the treatment efficacy for patients with HCC. Camrelizumab, a PD1 inhibitor, has already received approval from the National Medical Products Administration (NMPA) for first-line treatment of advanced HCC. In a clinical trial, the objective response rate and 6-month overall survival rate of camrelizumab alone for HCC were reported as 14.7% and 74.4%, respectively[8]. However, combining camrelizumab with other treatments, such as apatinib, tyrosine kinase inhibitors, and radiotherapy, has shown promising results in significantly improving the efficacy of HCC as a first-line treatment[9-11]. Furthermore, several clinical studies[11,12] reported that camrelizumab plus TACE resulted in a better survival benefit for patients with HCC compared to camrelizumab or TACE alone. However, the combination of camrelizumab and TACE is still not widely adopted in the first-line treatment of HCC, as the efficacy and safety of the combination therapy for HCC remains controversial.

Therefore, we conducted the first meta-analysis to evaluate the survival outcomes, disease response, and safety of combining camrelizumab with TACE in the treatment of unresectable HCC patients.

Materials and Methods

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines (PRISM)[13] (**Supplementary Table I**) and has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with identifier CRD42022369600.

Search Strategy

Three investigators searched four databases – Embase, PubMed, Web of Science, and Cochrane Library up –to June 1, 2023, for relevant literature. The main search terms were ("hepatocellular carcinoma" OR "liver cancer") AND "ocrelizumab" AND ("TACE" OR "transcatheter arterial chemoembolization"). The detailed search strategy is presented in **Supplementary Table II**. We also checked the relevant references from the eligible studies.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) either prospective or retrospective clinical studies; (2) patients were clinically or pathologically diagnosed with primary or recurrent HCC; (3) the patient with HCC was treated with TACE and camrelizumab simultaneously or sequentially; (4) at least one of the following primary outcomes were reported in the studies: complete response (CR), objective response rate (ORR), disease control rate (DCR), the treatment-related adverse events (AEs), overall survival (OS) and progression-free survival (PFS). (5) the efficacy was evaluated based on the Response Evaluation Criteria for Solid Tumors guidelines, Version 1.1 (RECIST 1.1).

The exclusion criteria were: (1) duplicated papers; (2) the patient had HCC and other malignancies at the same time; (3) the types of articles included case reports, reviews, letters, conference abstracts, editorials; (4) experiments conducted in *vitro* or animals instead of patients; (5) the exact data cannot be extracted from the article; (6) non-English-written literature.

Data Extraction

Three reviewers (FX, XS, and JB) collected necessary data independently from the selected studies. Any issues encountered during the data extraction process were resolved through negotiation or the judgment of a third reviewer. The detailed information that we need to gather included the first author's name, country of origin, published year, type of trials, trial design, sample

size, age, sex, disease stage, treatment regimens, follow-up time, treatment-related AEs, grade ≥3 and serious AEs, efficacy parameters [CR, partial response (PR), stable disease (SD), progressive disease (PD), ORR and DCR], survival endpoints OS and PFS. Survival endpoints were collected as hazard ratio (HR) with a 95% confidence interval (CI). If the HR was directly obtained difficulty, the data could be extracted from the Kaplan-Meier curves using the software Engauge Digitizer version 12.1 (Boston, MA, USA).

Quality Assessment

The majority of the studies included were single-arm studies and non-randomized controlled trials (NRCT), so the methodological quality of all included studies was assessed using the Methodological Index for Nonrandomized Studies (MINORS)[14]. The items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). Both single-arm trials with scores ≥8 and nonrandom comparative studies with scores ≥13 were considered high-quality reports; otherwise, the studies were of low quality.

Statistical Analysis

All data analyses were conducted using Review Manager version 5.3 (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark), and Stata Software version 14.0 (StataCorp Station, TX). The RDs with 95% CI were pooled to evaluate the AEs, CR, ORR, and DCR of patients treated with camrelizumab combined with TACE in single-arm studies and RRs for comparative trials. The pooled HRs with 95% CI were used to assess the OS and PFS. The heterogeneity was evaluated using Cochran's Q and I^2 statistics for each outcome. The studies were considered without heterogeneity when $p>0.10$ or $I^2<50\%$, then the fixed-effects model was used to pool the effects; otherwise, subgroup analyses or random-effects models were selected. Publication bias was estimated through the Funnel plot and Egger's test, and the p-value <0.05 indicated statistical significance.

Results

Studies Selection

A total of 122 trials were identified after a preliminary search from the databases and imported into the document management software EndNote X9 (Thomson Corporation, CT, USA). Subsequently, we excluded 60 duplicates and 38 records after screening the titles and abstracts and removed 7 records after reading the full text. Ultimately, a total of 17 studies[10,15-30] involving 1,377 cases were included according to the exclusion and inclusion criteria. The PRISMA flow diagram of study selection is shown in Figure 1.

Study Characteristics and Quality Assessment

All studies were conducted in China. Of the 17 included studies, there were 10 single-arm trials[10,15,16,18,19,21-23,25,26], six nonrandomized comparative trials[17,24,27-30], and an RCT trial[20]. The cases in 14 studies[10,16,18,19,21-30] had advanced HCC, and the cases in other trials[15,17,20] had unresectable initial treatment HCC. Moreover, six comparative studies[17,24,27-30] reported the survival data, and two sets of survival data were extracted from one comparative trial[24] according to before and after propensity score matching (PSM). The quality of the included studies was estimated using MINORS, and all studies were high-quality. The characteristics and the MINORS scores of the included studies are shown in Table I. The detailed quality scores of the studies are in **Supplementary Table III**.

Efficacy Outcomes

All included studies have reported the efficacy effects. The pooled CR rate, ORR and DCR were 0.08 (95% CI: 0.01-0.15, p=0.03; I^2=0%, p=1.00), 0.47 (95% CI: 0.42-0.52, p<0.00001; I^2=8%, p=0.35), and 0.82 (95% CI: 0.77-0.88, p<0.00001; I^2=0%, p=0.381), respectively (Figure 2A-C). Furthermore, seven trials[17,20,24,27-30] were retrieved to compare the efficacy of treatment based on TACE plus camrelizumab *vs.* treatment without TACE or camrelizumab. The pooled effects showed that the CR rate of the TACE plus camrelizumab group was higher than the control group (RR=1.61, 95% CI: 1.27-2.04, p<0.0001; I^2=34%, p=0.17) (Figure 3A). Similarly, the ORR and DCR of the combination treatment were 1.56 times (95% CI: 1.19-2.05, p=0.001; I^2=63%, p=0.01) and 1.55 times (95% CI: 1.19-2.03, p=0.001; I^2=63%, p=0.01) higher than those of the control group (Figure 3B-C), respectively, and the random model was used for the analyses since there was slight heterogeneity among the seven studies[17,20,24,27-30] for the ORR and DCR.

In addition, five comparative trials[17,24,27,29,30] involving 728 cases reported the OS, and four trials[24,27,28,30] involving 657 cases reported the PFS. The pooled effects showed that the OS of patients treated with regimens based on TACE + camrelizumab was longer than those treated with-

Table I. Characteristics of included trails.

First author	Year	Study type	Sample size (male/female)	Age (median)	Follow-up time (median)	HCC	Interventions		Endpoint	NOS score
							Experiment group	Control group		
Wang et al[15]	2022	Single-arm retrospective	89 (75/14)	54.2	16 months	Unresectable initial treatment	TACE+camrelizumab +apatinib	NA	CR, ORR, DCR, AEs	13
Ren et al[16]	2022	Single-arm retrospective	41 (32/9)	54.2	24 months	advanced	TACE+camrelizumab	NA	CR, ORR, DCR, AEs	12
Ju et al[17]	2022	Comparative retrospective	56 (46/10)	52	13.5 months	unresectable initial treatment	TACE+camrelizumab+apatinib	Camrelizumab +apatinib	CR, ORR, DCR, AEs, OS	21
Huang et al[18]	2021	Single-arm retrospective	12 (10/2)	54.5	NA	advanced	TACE+camrelizumab +sorafenib+SBRT	NA	ORR, DCR, AEs	12
Liu et al[19]	2021	Single-arm retrospective	22 (17/5)	57.7	NA	advanced	TACE+camrelizumab+lenvatinib	NA	CR, ORR, DCR, AEs	12
Zhang et al[20]	2022	RCT prospective	46 (29/17)	57.16	12 months	unresectable initial treatment	TACE+camrelizumab	TACE	CR, ORR, DCR, AEs	21
You et al[21]	2022	Single-arm prospective	101 (89/12)	56.8	NA	advanced	ACE+camrelizumab	NA	CR, ORR, DCR, AEs	12
Zhang et al[22]	2022	Single-arm retrospective	38 (30/8)	54	NA	advanced	TACE+camrelizumab+apatinib	NA	CR, ORR, DCR, AEs	12
Ren et al[23]	2022	Single-arm retrospective	54 (45/9)	53.5	11 months	advanced	TACE+camrelizumab	NA	CR, ORR, DCR, AEs	13
Sun et al[24]	2023	Comparative retrospective	123 (106/17)	53.8	NA	advanced	TACE+camrelizumab+TKIs	TACE+TKIs	CR, ORR, DCR, AEs, OS, PFS	21
Jun et al[25]	2022	Single-arm retrospective	80 (66/14)	52.7	14.6 months	advanced	TACE+camrelizumab+apatinib	NA	CR, ORR, DCR, AEs	14
Yin et al[26]	2023	Single-arm retrospective	113 (87/26)	52	NA	advanced	TACE+camrelizumab	NA	ORR, DCR, AEs	12
Sun et al[27]	2023	Comparative retrospective	31 (25/6)	58.63	14.2 months	advanced	TACE+camrelizumab+lenvatinib	TACE+lenvatinib	CR, ORR, DCR, AEs, OS, PFS	22
Zhang et al[10]	2022	Single-arm retrospective	34 (30/4)	54.84	10.6 months	advanced	TACE+camrelizumab+ICIs	NA	CR, ORR, DCR, AEs,	11
Guo et al[28]	2022	Comparative retrospective	20 (19/1)	56	12 months	advanced	TACE+camrelizumab	TACE	CR, ORR, DCR, AEs, PFS	19
Zhu et al[29]	2022	Comparative prospective	34 (29/5)	50.3	NA	advanced	TACE+camrelizumab+apatinib	TACE+apatinib	CR, ORR, DCR, AEs, OS	22
Duan et al[30]	2023	Comparative retrospective	483 (399/84)	52.6	16.3 months	advanced	TACE+camrelizumab+apatinib	TACE+apatinib	CR, ORR, DCR, AEs, OS, PFS	22

NA: Not available, RCT: randomized control trials HCC: hepatocellular carcinoma, TACE: transcatheter arterial chemoembolization, CR: complete response, ORR: objective response rate, DCR: disease control rate, AEs: adverse events, OS: overall survival, PFS: progression-free survival.

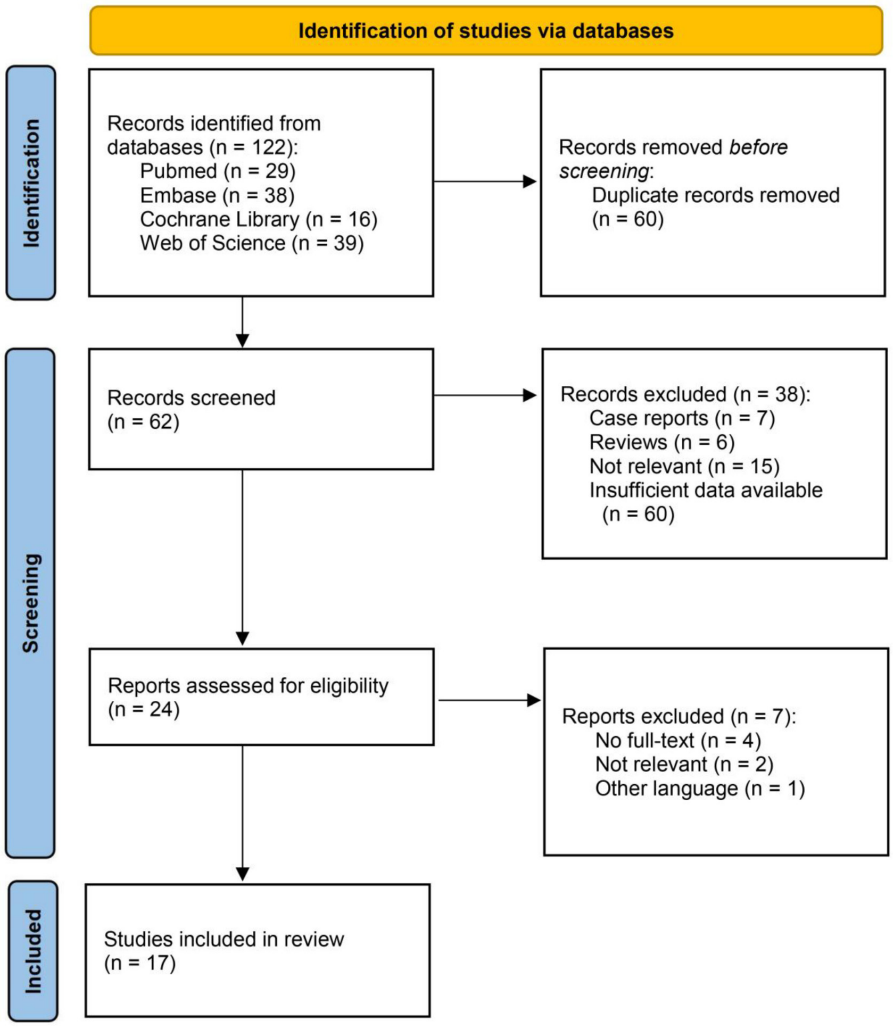

Figure 1. Flow diagram of study selection.

out TACE or camrelizumab (HR=2.60, 95% CI: 2.25-3.02, $p<0.00001$; $I^2=46\%$, $p=0.10$) (Figure 4A). The results also indicated that regimens based on TACE + camrelizumab could notably prolong the PFS of patients with HCC (HR=4.90, 95% CI: 1.94-12.38, $p=0.0008$; $I^2=0\%$, $p=0.87$) (Figure 4B).

Safety Outcomes

The treatment-related AEs were reported in all included studies. The results showed that the pooled all AEs rate was 0.77 (95% CI: 0.65-0.89, $p<0.00001$) through the random-effect model, while the severe AEs (over 3 grade) rate was only 0.29 (95% CI: 0.22-0.36, $p<0.00001$). Those trials reported more than 29 AEs, and the most common AEs, in order, were pain (such as muscle pain, pectoralgia) (RD=0.47, 95% CI: 0.33-0.61, $p<0.00001$), fever (RD=0.46, 95% CI: 0.34-0.58, $p<0.00001$), hepatic function abnormalities (RD=0.44, 95% CI: 0.20-0.68, $p=0.0004$), hypoalbuminemia (RD=0.39, 95% CI: 0.08-0.70, $p=0.01$) and hypertension (RD=0.37, 95% CI: 0.31-0.44, $p<0.00001$). Besides, there were several AEs with low incidence and no statistical significance ($p>0.05$), including pneumonitis, myocarditis, lymphopenia, liver abscess, joint pain, gingival bleeding, and dysphonia. Furthermore, in some comparative studies[17,30], the incidence of hepatic encephalopathy and nausea in TACE plus camrelizumab were significantly higher in patients treated with TACE plus Carelizumab compared to those received regimens without TACE or camrelizumab, and the pooled effects were

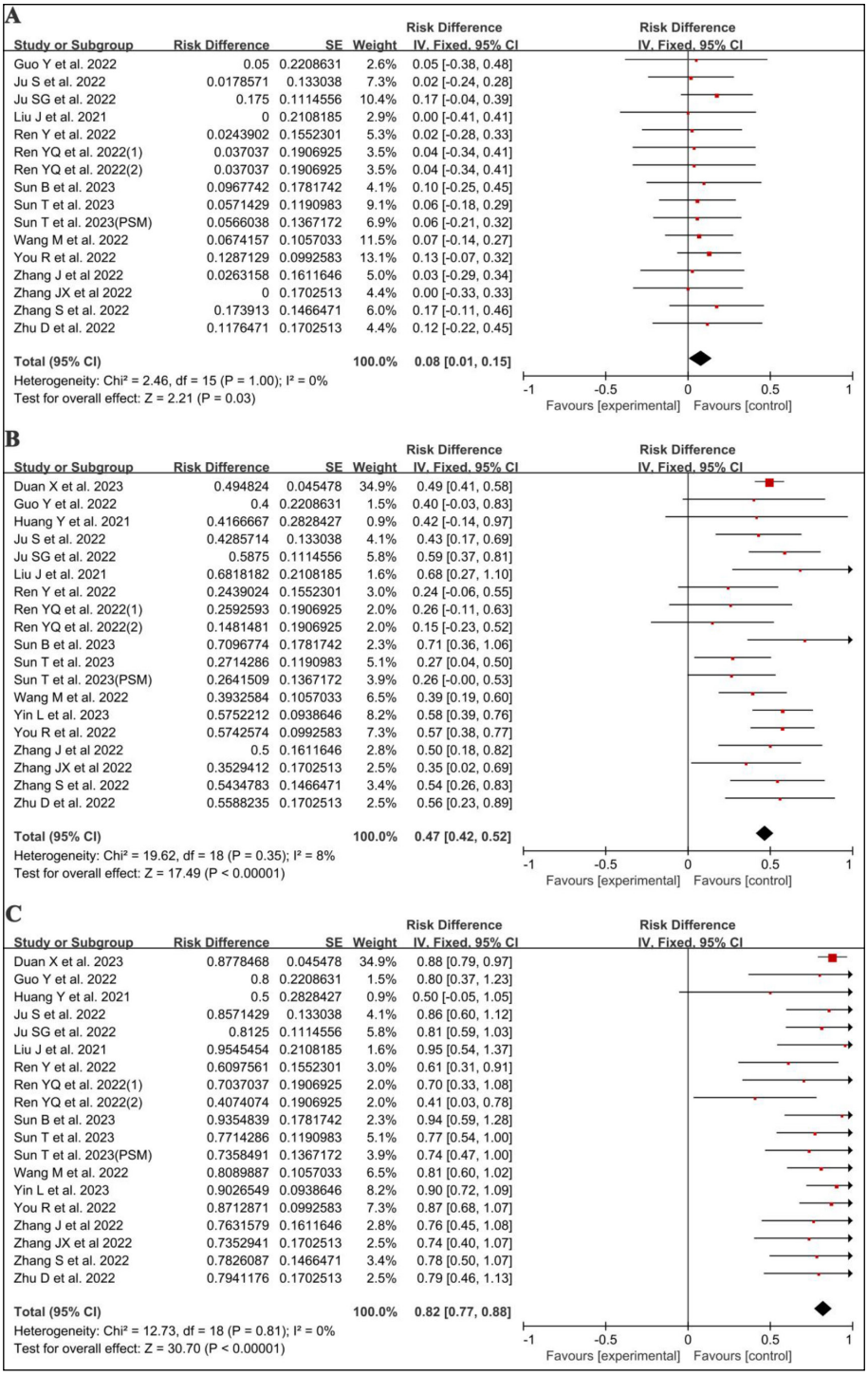

Figure 2. Forest plot of response rate for the treatment based on TACE combined with camrelizumab. **A**, The forest plot of CR rate; (**B**) the forest plot of ORR; (**C**) the forest plot of DCR.

4.29 (95% CI: 2.51-07.35, $p<0.00001$) and 1.35 (95% CI: 1.13-1.61, $p=0.001$), respectively. Remarkably, there was no obvious difference in the incidence of other AEs between the experimental group and the control group ($p>0.05$). The specific results of pooled AEs can be found in Table II; the main forest plots are shown in **Supplementary Figure 1**.

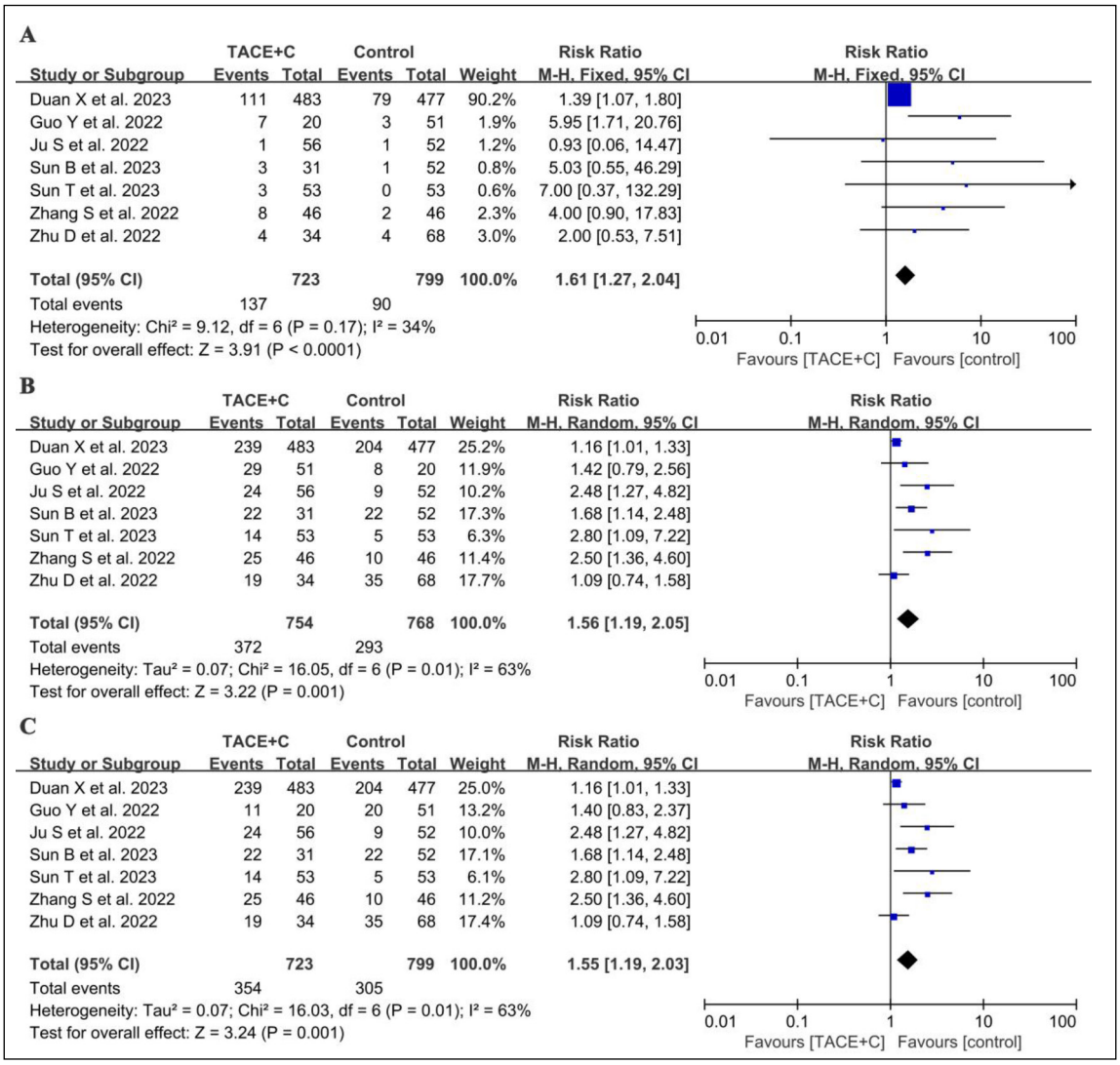

Figure 3. Forest plot of response rate of the comparison between the treatment based on TACE plus camrelizumab *vs.* treatment without TACE or camrelizumab. **A**, The forest plot of CR; (**B**) the forest plot of ORR; (**C**) the forest plot of DCR. TACE+C: TACE + camrelizumab; control group: the patients were treated without TACE or camrelizumab.

Sensitivity Analysis

Sensitivity analyses were conducted to evaluate the stability of the results from the analysis, including the pooled CR rate, ORR, DCR, OS, PFS, and the rate of all AEs, by individually removing each study and then merging the effect quality. The analysis results showed that excluding any individual study had no significant impact on the pooled effects, indicating stability and no significant deviation in the pooled results. This suggests our combined results were reliable (Figure 5).

Publication Bias

The potential publication bias was assessed through the funnel plots and Egger's test. The funnel plots showed that the left and right of CR, ORR, DCR, all AEs, OS, and PFS were symmetric (Figure 6). Besides, Egger's test showed that all *p*-values were more than 0.1, indicating that there was a low probability of publication bias among the included literature.

Discussion

Both camrelizumab and TACE have been utilized as first- and second-line treatments for patients with advanced HCC, showing the potential benefits of immunotherapy in the management of this disease. However, the clinical and safety out-

Table II. Adverse events after the treatment based on TACE plus carelizumab.

	The rate of treatment-related AEs			AEs of treatment *vs.* control group		
	RD and 95% CI	*p*-value	Heterogeneity	RR and 95% CI	*p*-value	Heterogeneity
All AEs	0.77 [0.65, 0.89]	**<0.00001**	p=0.01, I^2=63%	1.00 [0.95, 1.05]	1.00	p=0.45, I^2=0%
Severe AEs	0.29 [0.22, 0.36]	**<0.00001**	p=0.08, I^2=44%	1.24 [0.90, 1.71]	0.18	p=0.11, I^2=54%
Anemia	0.26 [0.13, 0.39]	**<0.0001**	p=0.44, I^2=0%	NR	NR	NR
Decreased appetite	0.12 [0.05, 0.19]	**0.0007**	p=0.44, I^2=0%	0.78 [0.60, 1.02]	0.07	p=0.49, I^2=0%
Diarrhea	0.20 [0.13, 0.27]	**<0.00001**	p=0.98, I^2=0%	1.14 [0.93, 1.42]	0.21	p=0.59, I^2=0%
Dysphonia	0.25 [-0.03, 0.52]	0.08	p=0.01, I^2=73%	NR	NR	NR
Fatigue	0.27 [0.21, 0.32]	**<0.00001**	p=0.47, I^2=0%	1.19 [0.83, 1.70]	0.34	p=0.06, I^2=60%
Fever	0.46 [0.34, 0.58]	**<0.00001**	p=0.007, I^2=57%	1.27 [0.87, 1.84]	0.21	p=0.003, I^2=81%
Gastrointestinal hemorrhage	0.09 [0.01, 0.16]	**0.02**	p=0.95, I^2=0%	0.93 [0.65, 1.33]	0.70	p=0.64, I^2=0%
Gastrointestinal reaction	0.32 [0.25, 0.40]	**<0.00001**	p=0.83, I^2=0%	1.06 [0.89, 0.27]	0.50	p=0.69, I^2=0%
Gingival bleeding	0.12 [-0.03, 0.27]	0.13	p=0.55, I^2=0%	NR	NR	NR
Hand-foot skin reaction	0.31 [0.25, 0.37]	**<0.00001**	p=0.13, I^2=33%	0.85 [0.74, 0.97]	**0.01**	p=0.47, I^2=0%
Hepatic encephalopathy	0.13 [0.05, 0.21]	**0.001**	p=0.65, I^2=0%	4.29 [2.51, 7.35]	**<0.00001**	p=0.79, I^2=0%
Hepatic function abnormalities	0.44 [0.20, 0.68]	**0.0004**	p=0.003, I^2=72%	1.06 [0.72, 1.56]	0.77	p=0.86, I^2=0%
Hypertension	0.37 [0.31, 0.44]	**<0.00001**	p=0.46, I^2=0%	1.02 [0.90, 1.15]	0.77	p=0.49, I^2=0%
Hypoalbuminemia	0.39 [0.08, 0.70]	**0.01**	p=0.04, I^2=76%	NR	NR	NR
Joint pain	0.20 [-0.01, 0.40]	0.06	p=0.75, I^2=0%	NR	NR	NR
Leukopenia	0.29 [0.16, 0.42]	**<0.0001**	p=0.29, I^2=20%	1.24 [0.63, 2.44]	0.53	p=0.31, I^2=4%
Liver abscess	0.03 [-0.05, 0.10]	0.52	p=1.00, I^2=0%	1.68 [0.72, 3.88]	0.23	p=0.74, I^2=0%
Lymphopenia	0.14 [-0.09, 0.37]	0.24	p=0.95, I^2=0%	NR	NR	NR
Myocarditis	0.02 [-0.05, 0.09]	0.63	p=1.00, I^2=0%	NR	NR	NR
Nausea	0.34 [0.20, 0.47]	**<0.00001**	p=0.005, I^2=60%	1.35 [1.13, 1.61]	**0.001**	p=0.84, I^2=0%
Neutropenia	0.31 [0.16, 0.45]	**<0.0001**	p=0.30, I^2=18%	NR	NR	NR
Pain	0.47 [0.33, 0.61]	**<0.00001**	p=0.03, I^2=56%	1.03 [0.91, 1.16]	0.69	p=0.75, I^2=0%
Pneumonitis	0.02 [-0.05, 0.10]	0.59	p=1.00, I^2=0%	NR	NR	NR
Proteinuria	0.18 [0.12, 0.24]	**<0.00001**	p=0.76, I^2=0%	0.93 [0.74, 1.17]	0.56	p=0.54, I^2=0%
Rash	0.15 [0.09, 0.21]	**<0.00001**	p=0.40, I^2=5%	1.56 [0.59, 4.11]	0.37	p=0.003, I^2=88%
RCCP	0.35 [0.21, 0.48]	**<0.00001**	p<0.001, I^2=76%	6.89 [0.41, 115.15]	0.18	p<0.001, I^2=93%
Stomatitis	0.16 [0.08, 0.24]	**<0.0001**	p=0.52, I^2=76%	1.10 [0.85, 1.43]	0.48	p=0.79, I^2=0%
Thrombocytopenia	0.14 [0.06, 0.21]	**0.0003**	p=0.70, I^2=0%	0.96 [0.73, 1.24]	0.74	p=0.43, I^2=0%
Thyroid dysfunction	0.10 [0.04, 0.17]	**0.0009**	p=1.00, I^2=0%	NR	NR	NR

RCCP: reactive cutaneous capillary endothelial proliferation; RD: risk difference; RR: risk ratio; NR: not reported.

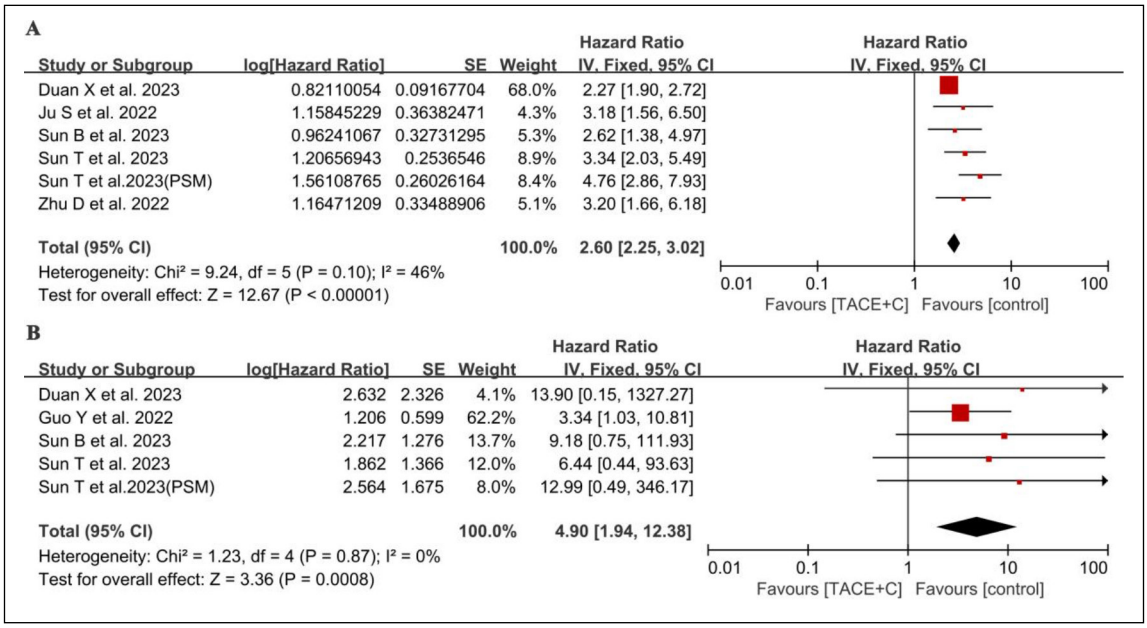

Figure 4. Forest plot of survival analyses for treatment based on TACE plus camrelizumab. **A**, the forest plot of OS; (**B**) the forest plot of PFS. TACE+C: TACE + camrelizumab; control group: the patients treated without TACE or camrelizumab.

comes of combining camrelizumab with TACE in HCC have not been comprehensively estimated. This meta-analysis is the first study to summarize the efficacy and safety of the combination of TACE and camrelizumab for HCC.

In this study, the pooled CR rate for the combination therapy was 8.0%, which was nearly 1.61 times higher than the CR rate for the treatment without camrelizumab or TACE in the comparative trials. This result aligns with the finding reported by Yuan et al[31], where the CR rate of TACE monotherapy in HCC patients was 1.7%. Furthermore, the overall ORR and DCR were 47% and 82%, respectively, which were 1.56 and 1.55 times higher than the control groups in comparative studies[17,20,24,27-30]. Notably, Yuan et al[31] also found that the ORR of TACE as monotherapy for HCC was 7.8%, which is significantly lower than the 47% in our study. PD1 inhibitors used as monotherapy have shown limited efficacy in the systemic treatment of HCC[32]. However, based on the data provided, the patients with HCC could achieve a better disease response rate from the combination of camrelizumab and TACE compared to the control group. Besides, the survival effects were extracted from the five trials, and the results showed that the combination regimen yielded an improvement in the OS (HR=2.60, 95% CI: 2.25-3.02, p<0.00001) and PFS (HR=4.90, 95% CI: 1.94-12.38, p=0.0008) compared with the control group, indicating that the treatment for HCC could significantly extend HCC patient's survival. Many clinical studies[12,31,33-35] reported that the combination treatments based on the TACE or PD1 inhibitors remarkably prolonged the OS and PFS when compared to TACE or PD1 inhibitors monotherapies. For example, TACE combined with targeted therapy and immunotherapy group showed significantly better OS (not reached *vs.* 10.4 months) and PFS (14.8 *vs.* 2.3 months) than the TACE group. Moreover, Yang et al[33] reported that the patients with HCC who received regorafenib plus ICIs and TACE had a higher ORR (34.8% *vs.* 4.3%), a longer PFS (5.8 *vs.* 2.6 months), and a longer OS (15 *vs.* 7.5 months) than those who received regorafenib plus ICIs. Based on previous studies[5,8] and our analysis, the results collectively show excellent efficacy in terms of using TACE plus camrelizumab combination treatment compared with treatment without TACE or camrelizumab.

Nevertheless, our analysis showed that the camrelizumab plus TACE combination therapy could induce multiple treatment-related adverse effects. The incidence of overall AEs was 77%, and grade 3/4 grade AEs were 29%, meaning that the combination therapy can lead to a higher incidence of adverse effects. The toxic effects were

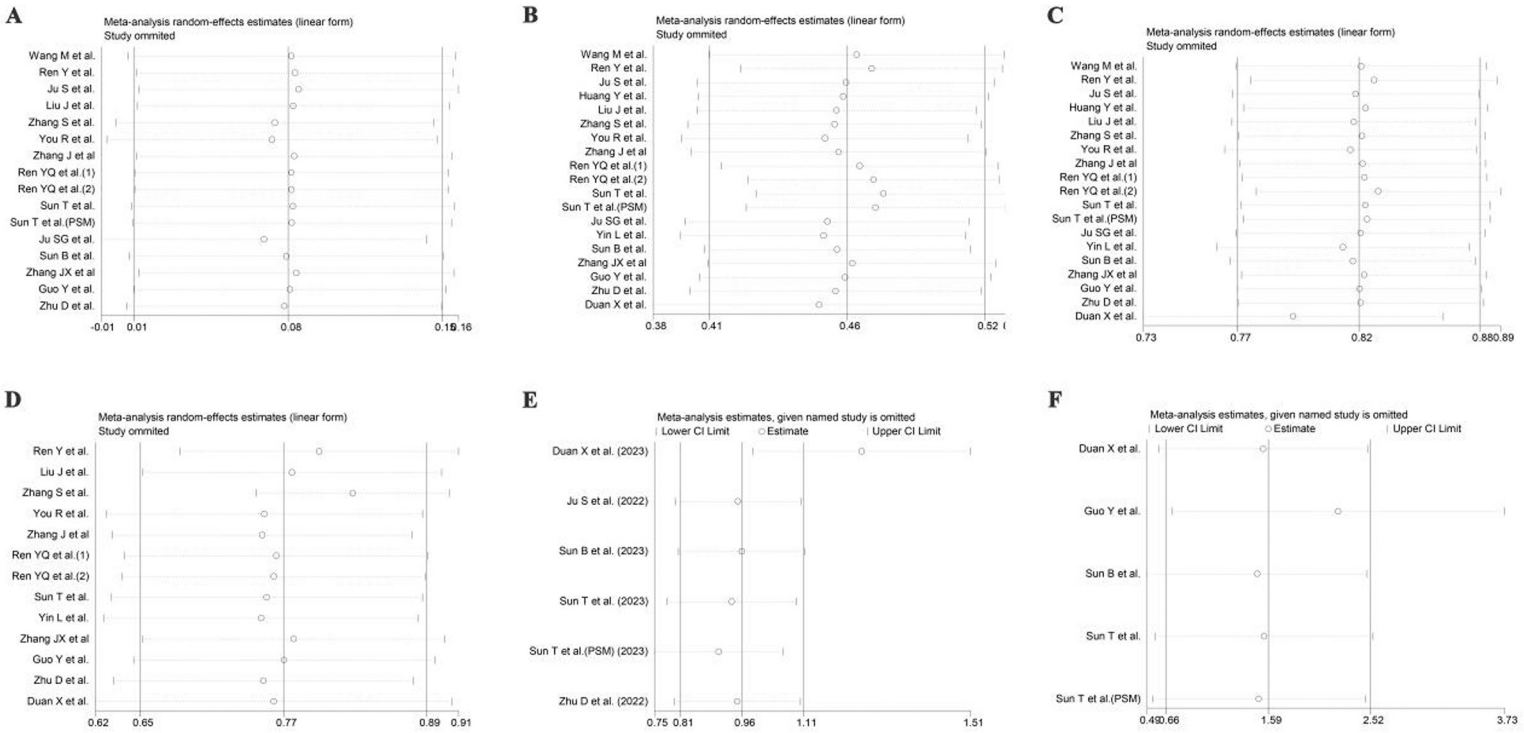

Figure 5. Sensitivity analysis of the meta-analysis. **A**, CR in TACE plus camrelizumab group; (**B**) ORR in TACE plus camrelizumab group; (**C**) DCR in TACE plus camrelizumab group; (**D**) all AEs in TACE plus camrelizumab group; (**E**) OS in TACE plus camrelizumab group; (**F**) PFS in TACE plus camrelizumab group.

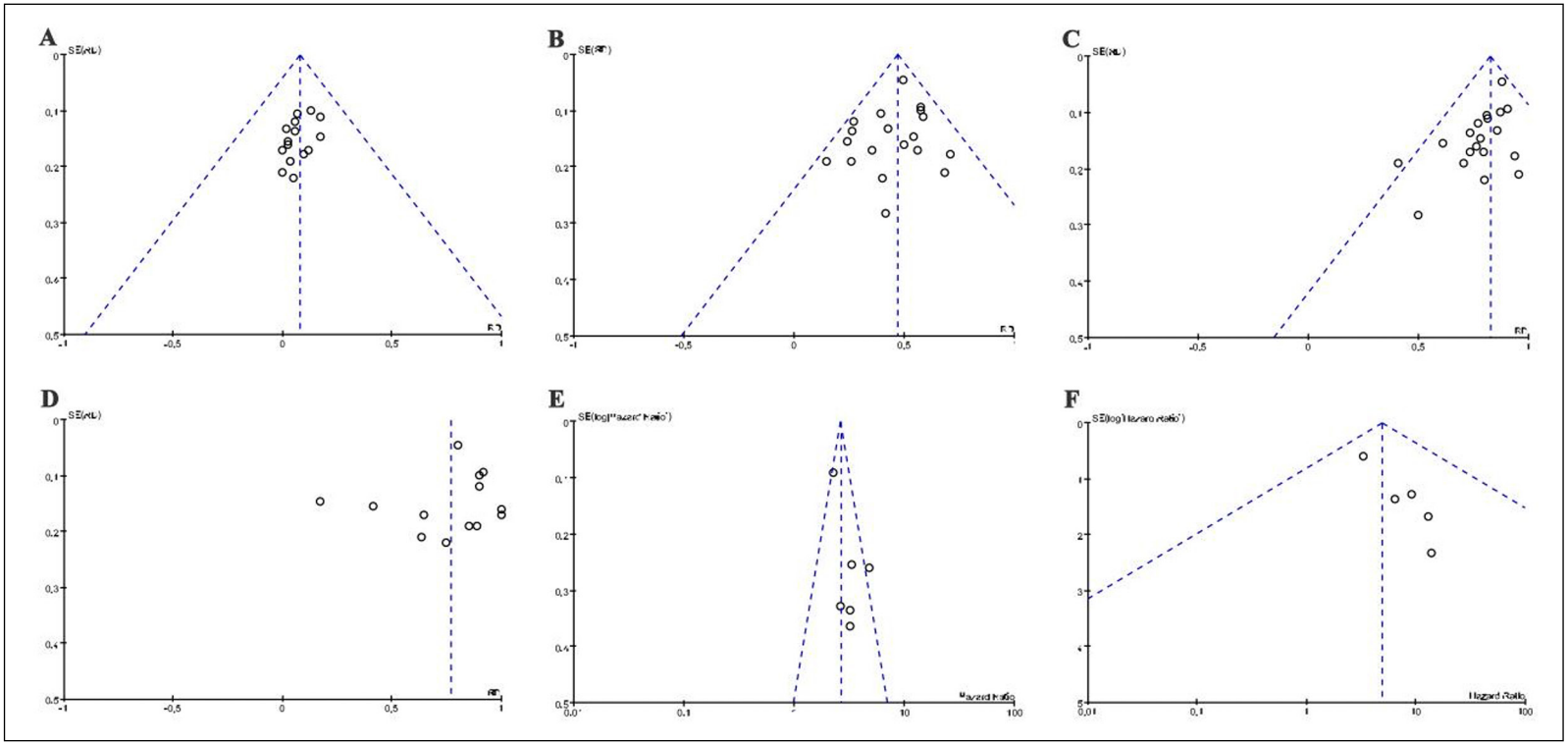

Figure 6. Eggre's funnel plots for the studies involved in the meta-analysis. **A**, CR in TACE plus camrelizumab group; (**B**) ORR in TACE plus camrelizumab group; (**C**) DCR in TACE plus camrelizumab group; (**D**) AEs in TACE plus camrelizumab group; (**E**) OS; (**F**) PFS.

mainly focused on the following areas: myelosuppression, gastrointestinal reaction, liver function abnormalities, immune-related disorders, and others (fatigue, dysphonia, joint pain, pain, thyroid dysfunction). The most common AEs included fever (46%), hepatic function abnormalities (44%), pain (47%), hypoalbuminemia (39%), hypertension (37%), and reactive cutaneous capillary endothelial proliferation (RCCP) (35%). According to previous studies[8,9], most of these AEs were caused by camrelizumab. AEs reported by Qin et al[8] and Fang et al[34] were similar to our study. In that clinical study[8], grade 3 or 4 camrelizumab-related AEs occurred at 22%, and the most common AEs were RCCP (67%), proteinuria (24%), increased alanine aminotransferase (23%), and increased aspartate aminotransferase (26%). Meanwhile, the main AEs of TACE for HCC were abnormal liver function[35]. However, the camrelizumab plus TACE combination therapy group could increase the probability of hepatic encephalopathy (HR=4.29, 95% CI: 2.51-7.35, $p<0.00001$) and nausea (HR=1.35, 95% CI: 1.13-1.61, $p=0.001$) relative to the control group, while no difference was found in other AEs between two groups.

The research results indicated that TACE + camrelizumab treatments showed promising efficacy and manageable toxicity in patients with unresectable HCC. Several possible explanations exist for this finding: (1) TACE induces tumor cell necrosis and neoangiogenesis, whereas TACE-induced immune tolerance can be attenuated by PD-1 inhibitors[36]; (2) TACE induces an ischemic and hypoxic microenvironment leading to tumor necrosis and tumor-specific antigen release. The combination of PD1 inhibitors enhances the development of tumor antigen-specific memory T-cells and maintains the patient's antitumor response; (3) TACE leads to a hypoxic tumor microenvironment resulting in the upregulation of hypoxia-inducible factor-1α and basic fibroblast growth factor (*bFGF*). PD-1 inhibitors exert unique immunomodulatory effects by blocking *FGFR-4*, decreasing Treg differentiation, and inhibiting *TGFß* signaling, which in turn improves the immune tolerance status of the tumor microenvironment[37]. Besides, TACE can induce immunogenic cell death by releasing tumor antigens from dying cancer cells relying on the *eIF2A* phosphorylation-dependent exposure of endoplasmic reticulum chaperones such as calreticulin[38] and triggering damage-associated molecular patterns (such as adenosine triphosphate (ATP) release and type I interferon response)[39], which may improve the efficacy of immunotherapy.

To our knowledge, this is the first meta-analysis on the efficacy and safety of treatment based on camrelizumab plus TACE for HCC. However, this meta-analysis had several limitations. Firstly, although the number of trials was adequate, most studies were early-phase trials with a relatively small sample size. Besides, the risk of selection bias existed due to the small number of comparative studies included; the comparison of the advantages and disadvantages between treatment based on ocrelizumab plus TACE and the control group needs to be further analyzed in more controlled studies. Finally, because of the different types of treatment regimens, there was heterogeneity in the pooled effect.

Conclusions

Camrelizumab combined with TACE can be effective and safe in the short term for unresectable HCC. The combinational treatment also achieved better survival benefits than the regimens without TACE or camrelizumab and did not increase the incidence of toxicity profile. However, the common AEs, such as fever and hepatic function abnormalities, still require active monitoring and treatment.

Conflict of Interest

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

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Authors' Contributions

FX and GX designed the study. FX, XS, and JB screened the studies and extracted data. The quality of the evidence was assessed using FX, XS, and CZ. FX and XS analyzed and interpreted the data. FX and GZ prepared figures and drafted the manuscript. FX and GX contributed to reviewing and editing the manuscript. All authors have approved the final version of the article, including the authorship list. All authors contributed to the article.

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Ethics Approval
Not applicable.

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