SYSTEMATIC REVIEW AND META-ANALYSIS

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Comparing Safety and Efficacy of TACE + Apatinib in Combination with a PD-1 Inhibitor versus a Non-triple Therapy for Treating Advanced Primary Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: This meta-analysis was performed to compare the efficacy and safety of a triple therapy, involving transcatheter arterial chemoembolization (TACE) + apatinib combined with a programmed-cell death protein-1 (PD-1) inhibitor versus TACE + apatinib, a dual therapy with apatinib and PD-1 inhibitor, and TACE alone for the treatment of advanced primary hepatocellular carcinoma (HCC).

Methods: A computerized systematic search of databases, such as PubMed, Embase, the Cochrane Library, CNKI, Wanfang Data, and VIP e-Journals was performed to retrieve studies comparing TACE + apatinib combined with a PD-1 inhibitor versus a non-triple therapy for the treatment of advanced primary HCC. The literature search, quality assessment, and data extraction were performed independently by two researchers. Stata 16.0 software was employed to analyze the data. Heterogeneity was assessed utilizing the I^2 statistic and p-value, followed by conducting sensitivity analysis.

Results: A total of 2,352 patients were enrolled from 8 studies, including 900 patients in the triple therapy group of TACE + apatinib combined with a PD-1 inhibitor, 877 patients in the TACE + apatinib group, 52 patients in the apatinib + a PD-1 inhibitor group, and 112 patients in the TACE group. The results revealed that the objective response rate (ORR) was significantly higher in the triple therapy group of TACE + apatinib combined with a PD-1 inhibitor than that in the non-triple therapy group [odds ratio (OR)=2.47, 95% confidence interval (95%CI): 1.61-3.78]. Besides, disease control rate (DCR) was greater in the triple therapy group of TACE + apatinib combined with a PD-1 inhibitor than that in the non-triple therapy group (OR=1.87, 95%CI: 1.44-2.44). Patients in the triple therapy group experienced a significant extension of overall survival (OS) (HR=0.42, 95%CI: 0.36-0.49). In addition, there was no significant difference in the overall rate of adverse events (AEs) between the two groups (OR=1.05, 95%CI: 0.89-1.22).

Conclusions: Compared with the non-triple therapy group, the triple therapy group of TACE + apatinib combined with a PD-1 inhibitor outperformed in terms of tumor response and long-term survival with manageable AEs.

Key words: apatinib – TACE – PD-1 inhibitor – advanced primary hepatocellular carcinoma – efficacy – meta-analysis.

Abbreviations: AE: adverse event; CI: confidence interval; DCR: disease control rate; HCC: hepatocellular carcinoma; HIF-1: hypoxia-inducible factor-1; ICI: immune checkpoint inhibitors; NOS: NewcastleOttawa Scale; OR: odds ratio; ORR: objective response rate; OS: overall survival; PD-1: programmed-cell death protein-1; PD-L1: programmed death-ligand 1; PFS: progression-free survival; RCT: randomized controlled trials; TACE: transcatheter arterial chemoembolization; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR-2: VEGH receptor-2.

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the seventh most prevalent malignancy and stands as the second leading cause of cancer-related fatalities worldwide, with over half of these cases concentrated in China [1, 2]. The escalated occurrence of HCC in China is predominantly attributed to the heightened prevalence of risk factors linked to its etiology, such as hepatitis virus infection. Consequently, patients in this region frequently present with more severe disease characteristics, including multifocal involvement upon diagnosis [3-6].

Existing therapeutic approaches for HCC encompass surgical resection, liver transplantation, transarterial chemoembolization (TACE), ablation, systemic therapy, and supportive care [7, 8]. Regrettably, surgical interventions are viable for fewer than 20% of HCC patients at the time of diagnosis [9]. Therefore, non-surgical treatments (e.g., TACE) are particularly important in the management of HCC [10, 11]. Notably, TACE stands out as one of the most frequently utilized non-surgical treatments for patients with intermediate and advanced HCC.

The fundamental concept behind TACE involves the injection of chemotherapeutic drugs and embolic agents into the hepatic blood supply arteries to block the blood supply to the tumor. This process induces ischemia and hypoxia at the tumor site, thereby controlling the tumor growth with a proven track record of safety and efficacy [12-14]. Conversely, following TACE, local hypoxia triggers the activation of hypoxia-inducible factor-1 (HIF-1), upregulating the level of the vascular endothelial growth factor (VEGF). This leads to neo-angiogenic response or incomplete embolization after treatment, ultimately promoting tumor angiogenesis and recurrence [15-18]. Therefore, the combination of TACE and anti-angiogenic drugs has noticeably attracted clinicians' attention and has gradually demonstrated promising efficacy [19, 20].

Apatinib, one of the pioneering tyrosine kinase inhibitors (TKIs) developed in China, exerts highly selective action on VEGH receptor-2 (VEGFR-2), inhibiting c-Kit and c-Src tyrosine kinases [21, 22]. Administered at therapeutic doses, apatinib induces apoptosis in tumor cells that over express VEGFR-2, suppresses migration and proliferation of vascular endothelial cells, reduces tumor microvessel density, and inhibits tumor growth, thereby improving therapeutic efficacy [11, 13, 23-25]. Several studies have demonstrated that apatinib can improve the efficacy of TACE [11, 19, 26-29]. Furthermore, the liver's unique status as an immune-favorable organ, coupled with HCC being a prototypical inflammatory malignancy, makes it an ideal location for immune checkpoint inhibitors (ICIs) to exert their therapeutic effects [30]. In addition, programmed death-ligand 1 (PD-L1) expression in locally affected tumor cells and programmed-cell death protein-1 (PD1)/PD-L1 expression in the immune microenvironment's inflammatory cells significantly increase after TACE in HCC patients [31]. Studies, such as IMbrave150 and RESCUE, have conclusively shown that combining anti-angiogenic drugs with immunotherapy substantially enhances the efficacy of immunotherapy and improves patients' prognosis [32-34]. However, there remains a paucity of reports on the triple therapy approach comprising TACE + apatinib combined with a PD-1 inhibitor for advanced primary HCC, as well as the lack of evidence-based medical data.

Therefore, the present meta-analysis aimed to comprehensively evaluate the efficacy and safety of TACE + apatinib combined with a PD-1 inhibitor for the treatment of advanced primary HCC.

METHODS

Search Strategy

The study protocol was conducted according to PRISMA guidelines and registered in the PROSPERO database (Registration No. CRD42023439948) [35, 36]. A systematic search encompassed several databases, including PubMed, Embase, the Cochrane Library, CNKI, Wanfang Data, and VIP e-Journals, targeting studies published from October 2010 to July 2023. To ensure inclusivity, specific PD-1 inhibitor names were not employed as search terms. Finally, the following search terms were utilized: (liver neoplasms) OR (neoplasms, hepatic) OR (neoplasms, liver) OR (liver neoplasm) OR (neoplasm, liver) OR (hepatic neoplasms) OR (hepatic neoplasm) OR (neoplasm, hepatic) OR (cancer of liver) OR (hepatocellular cancer) OR (cancers, hepatocellular) OR (hepatocellular cancers) OR (hepatic cancer) OR (cancer, hepatic) OR (cancers, hepatic) OR (hepatic cancers) OR (liver cancer) OR (cancer, liver) OR (liver cancers) OR (cancers, liver) OR (cancers, liver) liver) OR (cancer of the liver) OR (cancer, hepatocellular) AND (TACE) AND (apatinib). In addition, the search was extended to include the clinical trial registry website (http://www.clinicaltrials.gov) and the China trial database (http://www.chictr.org.cn) to gather more specific information about registered studies. In cases where duplicate publications were identified for the same clinical trial, the most comprehensive and up-to-date study was selected. Furthermore, the reference lists of retrieved articles were reviewed to identify additional studies.

Study Selection

The screening process involved two sequential steps. First, titles, abstracts, and keywords of retrieved studies were utilized to exclude those that were irrelevant. Subsequently, all excluded studies underwent a full-text screening.

Inclusion criteria were 1) study subjects: patients diagnosed with medium-to-advanced primary HCC, as determined through imaging and/or pathological assessment, corresponding to BCLC stage B or C, and Child-Pugh stage A or B; 2) interventions: treatment involving TACE+apatinib+PD-1 inhibitor; 3) controls: studies involving controls receiving apatinib + TACE, apatinib PD-1 inhibitor, and TACE alone; 4) similar timing of apatinib administration between the two groups; 5) endpoints: studies must report at least one of the pre-determined endpoints for this investigation, accompanied by sufficiently detailed methods, patient population characteristics and survival data; 6) study design: randomized controlled trials (RCTs) and retrospective studies.

Exclusion criteria were 1) duplicate studies; 2) patients with concurrent combination of other tumors; 3) studies with unavailable full-text documents; 4) interventions involving hepatic arterial infusion chemotherapy (HAIC); 5) targeted therapy employing drugs other than apatinib (e.g., lenvatinib, sorafenib, etc.); 6) studies where no PD-1 inhibitors were administered in the study group; 7) duration of apatinib administration was <2 cycles; 8) poor-quality literature, including studies with substantial flaws in study design or those assessed as having a high risk of bias.

The eligibility of these studies was subsequently assessed independently by two investigators (D.P. and H.N.L.). In cases of disagreement, reassessment and discussion were initiated to arrive at a consensus based on the final results. If a resolution could not be reached even after reassessment, a third researcher (Z.X.H.) attempted to evaluate the eligibility of the study.

Data Extraction and Quality Assessment

For each study included in this analysis, two investigators (D.P. and H.N.L.) independently collected and recorded the following data: objective response rate (ORR), overall survival (OS), disease control rate (DCR), adverse events (AEs), author names, year of publication, type of study design, interventional details, type of TACE, dose of apatinib, and type and dose of PD-1 inhibitor. These data were systematically recorded in a data extraction form. Subsequently, an analysis was conducted based on the completed data extraction form. To assess the quality of the included studies, risk of bias was evaluated. Given that the selection process encompassed both RCTs and non-RCTs, the quality of non-RCTs was investigated using the Newcastle-Ottawa Scale (NOS). The NOS scale consists of three quality parameters: selection (0-4 points), comparability (0-2 points), and outcome assessment (0-3 points). The total quality scores for articles on the NOS scale range from 0 to 9, categorizing studies as low-quality (0 to 3 points), medium quality (4 to 6 points), or high-quality (> 7 points) [37].

Statistical Analysis

The relevant data were extracted and organized, and statistical analysis was performed by D.P. and H.N.L.. Meta-analysis was carried out using Stata 16.0 software (Stata Corp., College Station, TX, USA), and hazard ratios (HRs) and associated 95% confidence intervals (CIs) for OS were calculated. Estimated odds ratios (ORs) and their respective 95%CIs were also calculated for ORR, DCR, and AEs. To assess the degree of heterogeneity among the included studies, both the Q test and I^2 test were employed. A p value ≥0.05 or I^2≤50% indicated homogeneity of the findings. Heterogeneity was categorized as follows: low-heterogeneity (I^2<50%), moderate-heterogeneity (50%<I^2<75%), and high-heterogeneity (I^2>75%) [38]. When p<0.05 or I^2>50%, the random-effects model was utilized; otherwise, the fixed-effects model was used. In cases of high heterogeneity, sensitivity analysis and subgroup analysis were conducted to explore potential causes of heterogeneity. To assess the presence of publication bias, Begg's and Egger's tests were employed as assessment methods, in order to determine whether there were a sufficient number of eligible studies for a comprehensive analysis of publication bias.

RESULTS

Literature Search Results

The literature search was conducted across six databases, yielding a total of 478 studies. Of these studies, 217 duplicates were excluded, and two reviewers independently assessed the remaining 261 studies. Next, a total number of records were initially excluded during the screening of abstracts and titles (n=73). Subsequently, further studies were excluded for the following reasons: HAIC/targeted therapy involving other drugs or lacking PD-1 inhibitors (n=91); absence of a control group (n=25); insufficient data (n=20); unavailability of full-text (n=23); and following quality assessment (n=21). Finally, a total of 8 studies were included [39-46], and the detailed literature search process is illustrated in Fig. 1.

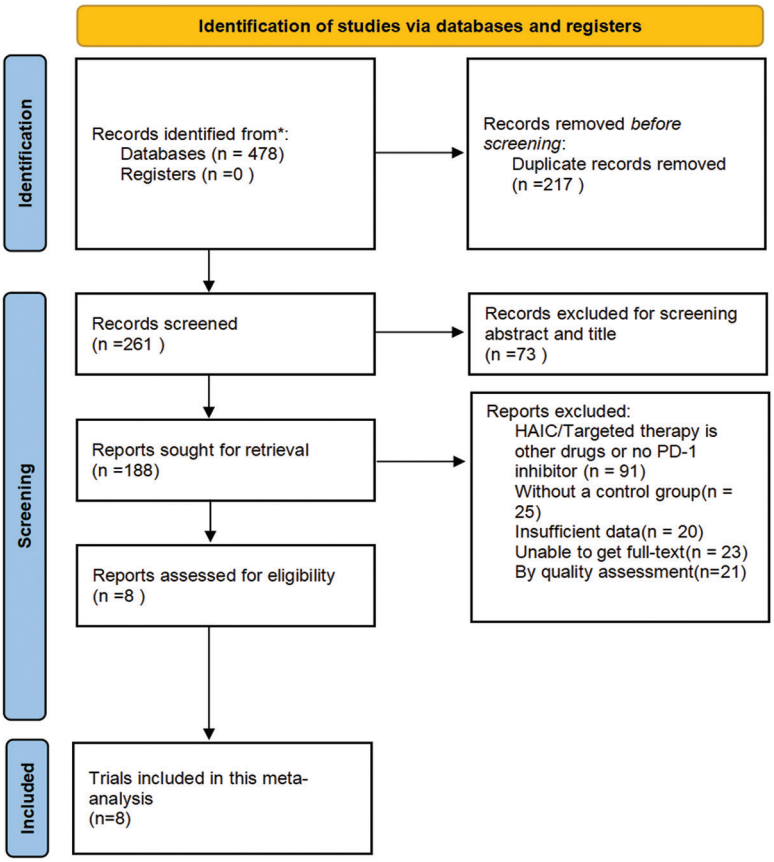

Fig. 1. Flowchart of the study selection.

Basic Characteristics and Quality Evaluation of the Included Studies

As the primary concentration was on evaluating the effectiveness of triple therapy involving TACE + apatinib combined with a PD-1 inhibitor for the treatment of advanced primary HCC, the type of PD-1 inhibitor was not specified. The characteristics of the studies ultimately included in the meta-analysis are presented in Table I. These studies were published between October 2010 and July 2023, and they were all conducted in China. The primary endpoints were ORR and OS; the secondary endpoint was DCR; and the safety endpoint was any grade of AEs. A total of 2,352 patients with advanced primary HCC were enrolled from 8 studies [39-46], of whom 900 cases were assigned to the triple therapy group of TACE + apatinib in combination with a PD-1 inhibitor, 877 cases were allocated to the TACE + apatinib group, 52 cases were assigned to the apatenib + PD-1 inhibitor group, and 112 cases allocated to the TACE group. All the studies were retrospective in nature, with five of them implementing propensity score matching (PSM) [41-45]. Two studies used drug-eluting beads TACE (DEB-TACE) approach for interventional embolization [39, 43], and 6 studies utilized camrelizumab as a PD-1 inhibitor [39, 40, 43-46]. In the control groups, 5 studies employed the regimen of apatinib + TACE [41-44, 46], one study used the combination of apatinib and a PD-1 inhibitor [39], 2 studies utilized TACE alone [40, 45]. The NOS scores [37] are detailed in Table II.

Primary Outcome Measures

The primary outcome measures for this meta-analysis were ORR and OS. It was found that 8 studies [39-46] with

Table I. The basic characteristics of the studies included in the meta-analysis

Study	Sample size	BCLC Stage %		Child–Pugh Class %		Study type	Study Group Program	Control Group Pro-gram	ORR	DCR	OS (m)	TACE regimen	Apatinib regimen	PD-1 inhibitors regimen	Types of PD-1 inhibitors	Score of NOS	Propensity score matching
		SG	CG	SG	CG												
Ju 2022 [39]	SG: 56 CG: 52	B: 13 C: 43	B: 5 C: 47	A: 77 B: 23	A: 79 B: 21	RS	A + C + TACE	A+C	24 vs 9	48 vs 30	24.8 vs 13.1	Adriamycin (60mg)	250 mg/d, 7 days after TACE	200mg /3W	C	6	No
Chen 2023 [40]	SG: 75 CG: 75	B: 77 C: 23	B: 71 C: 29	A: 60 B: 40	A: 67 B: 33	RS	A + C + TACE	TACE	73 vs 66	48 vs 28	11.24 ± 3.57 vs 15.38 ± 2.44	Lobaplatin (50 mg)	250 mg/d, 7 days after TACE	200mg /3W	C	6	No
Xia 2022 [41]	SG: 59 CG: 59	NA	NA	A: 95 B: 5	A: 97 B: 3	RS	A + P + TACE	A + TACE	37 vs 18	49 vs 47	22.5 vs 12	Adriamycin (50 ~ 70 mg)	250 mg/d, 3 days after TACE	200mg /3W	S/ C / T / Pe	8	Yes
Xia 2023 [42]	SG: 28 CG: 28	NA	NA	A: 93 B: 7	A:93 B: 7	RS	A + P + TACE	A + TACE	15 vs 5	23vs 21	14.6 vs 8.5	Adriamycin (50 ~ 70 mg)	250 mg/d, 3 days after TACE	200mg / 3W	S / C / T / Pe	7	Yes
Duan 2023 [43]	SG: 449 CG:449	B: 17 C: 83	B: 17 C: 83	A: 39 B: 61	A: 41 B: 59	RS	A + C + TACE	A + TACE	224 vs 191	397 vs 377	24.5 vs 18	Oxaplatin (100 mg) + Adriamycin /Epirubicin (40-60 mg) + Aclarubicin (20 -40mg)	250 mg/d, 3 days after TACE	200mg / 3W	C	8	Yes
Zhu 2022 [44]	SG: 34 CG: 68	B: 38 C: 62	B: 38 C: 62	A: 88 B: 12	A: 82 B: 18	RS	A + C + TACE	A + TACE	19 vs 35	27 vs 49	25.5 vs 18.5	Lobaplatin (30-50 mg) + Aclarubicin (10 - 30mg)	250 mg/d, 7 days after TACE	200mg / 3W	C	8	Yes
Jin 2023 [45]	SG: 84 CG:147	B: 33 C: 67	B: 35 C: 65	A: 85 B: 15	A: 87 B: 13	RS	A + C + TACE	TACE	50 vs 55	NA	24.1 vs 15.7	Adriamycin, Epirubicin, etc.	250 mg/d, 7 days after TACE	200mg / 3W	C	7	Yes
Liu 2023 [46]	SG: 37 CG: 39	B: 51 C: 49	B: 62 C: 39	A: 87 B: 13	A: 90 B: 10	RS	A + C + TACE	A + TACE	16 vs 8	25 vs 17	15.4 vs 11.3	Oxaplatin (50 -100mg)	250 mg/d, 3-7 days after TACE	200mg / 3W	C	8	No

A: apatinib; C: carilizumab; CG: control group; P: PD-1 inhibitor; RS: retrospective study; S: sindilizumab; SG: study group; Pe: pembrolizumab; TACE: transarterial chemoembolization; T: tislelizumab; W: week.

Table II. Quality assessment of the included studies using the NOS score

Study	Selection	Comparability	Outcome/Exposure	Global Score
Ju 2022, [39]	**	**	**	6
Chen 2023, [40]	**	**	**	6
Xia 2022, [41]	****	**	**	8
Xia 2023, [42]	****	**	*	7
Duan 2023, [43]	****	**	**	8
Zhu 2022, [44]	****	**	**	8
Jin 2023, [45]	****	**	*	7
Liu 2023, [46]	***	**	**	8

NOS: NewcastleOttawa Scale.

enrollment of 1,779 patients reported ORR of treatment. The ORR was higher in the triple therapy group of TACE + apatinib in combination with a PD-1 inhibitor than that in the non-triple group (OR=2.47, 95%CI: 1.61-3.78). Heterogeneity analysis indicated a moderate level of heterogeneity between studies (I^2=62.1%, p=0.010), necessitating the utilization of a random-effects model (Fig. 2).

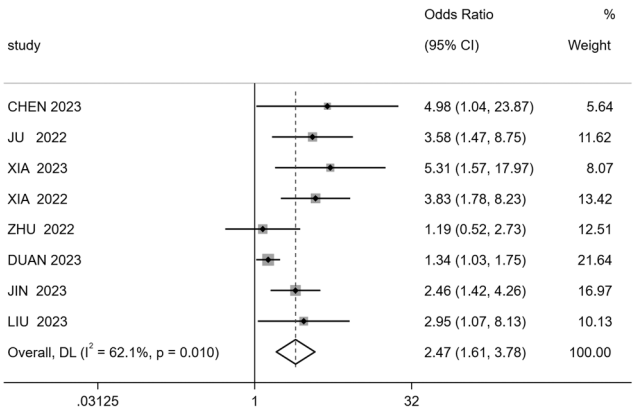

Fig. 2. Comparison of the objective response rate between the A+P+T (triple therapy) group and the non-triple therapy group for advanced HCC. A: apatinib; CI: confidence interval; D-L: DerSimonian and Laird; OR: odds ratio; P: PD-1 inhibitor; TACE: transarterial chemoembolization.

Moreover, 5 studies [39, 41, 43, 45, 46] involving a total of 1,395 cases reported data related to OS. The results revealed no significant heterogeneity (I^2=0%, p=0.726), and a fixed-effects model was therefore utilized. It was found that OS was longer in the triple therapy group of TACE + apatinib in combination with a PD-1 inhibitor than that in the control group (HR = 0.42, 95%CI: 0.36-0.49) (Fig. 3).

Secondary Outcome Measures

Secondary outcome measures included DCR and AEs. It was revealed that 7 studies [39-44, 46] reported DCR, involving a total of 1,516 patients. The results indicated that DCR was higher in the triple therapy group of TACE + apatinib combined with a PD-1 inhibitor than that in the non-triple group (OR=1.87, 95%CI: 1.44-2.44). Heterogeneity analysis exhibited a low level of heterogeneity between studies (I^2=28.3%, p=0.212), and a fixed-effects model was therefore utilized (Fig. 4).

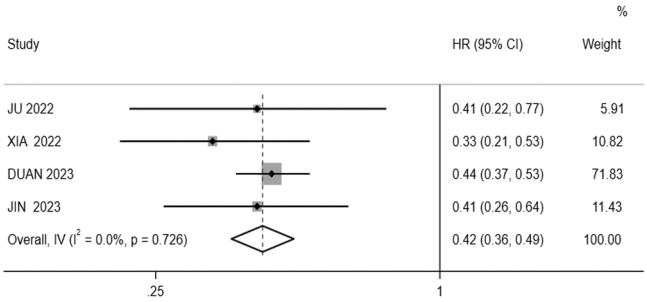

Fig. 3. Comparison of OS and associated 95% CIs for the A+P+T (triple therapy) group versus the non-triple therapy group in advanced HCC. HR: hazard ratio; I-V: inverse variance. For the rest of abbreviations see Fig. 2.

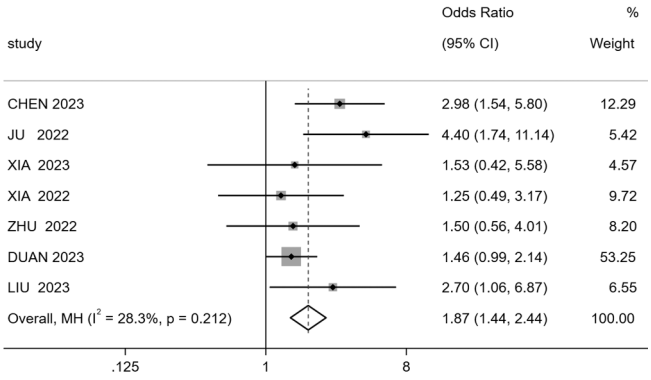

Fig. 4. Evaluation of disease control rate for the A+P+T (triple therapy) group versus the non-triple therapy group in advanced HCC. M-H, Mantel-Haenszel. For the rest of abbreviations see Fig. 2.

Among AEs of any grade, fever (OR=1.49, 95%CI: 0.82-2.70), pain (OR=1.09, 95%CI: 0.66-1.83), rash (OR=0.84, 95%CI: 0.62-1.15), fatigue (OR=0.98, 95%CI: 0.77-1.23), and hypertension (OR=1.01, 95%CI: 0.83-1.25) were not statistically significant. In addition, no statistically significant differences were found when comparing total AEs at any level (OR=1.05, 95%CI: 0.89-1.22) (Fig. 5). It was therefore concluded that the side effects were comparable between the study and control groups.

Heterogeneity Analysis

To analyze the reasons for the high heterogeneity of ORR, subgroup analysis was carried out based on the different

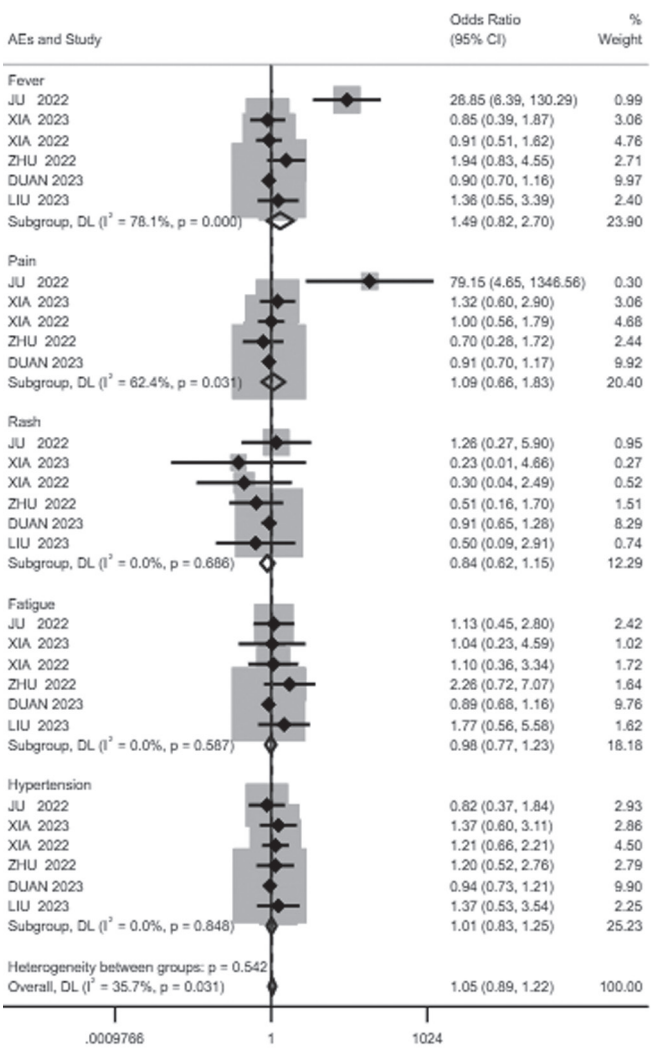

Fig. 5. Comparison of adverse events (AEs) between the triple therapy and non-triple therapy groups in advanced HCC. For abbreviations see Fig. 2.

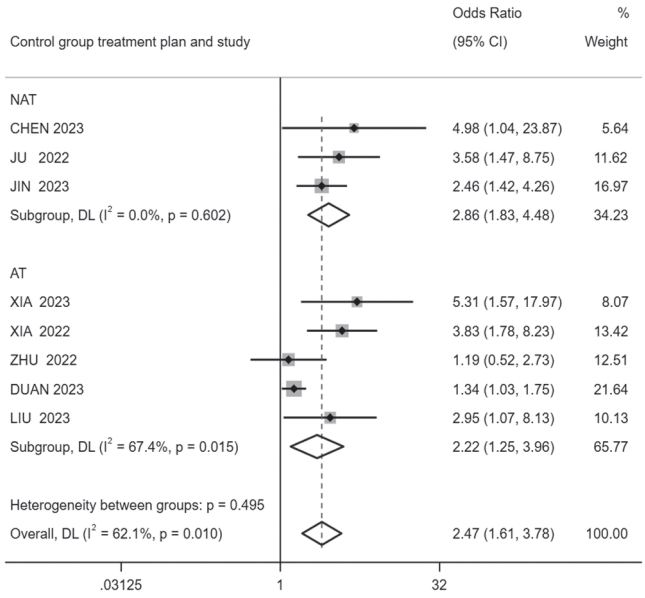

Fig. 6. Subgroup analysis of the combined objective response rate. AT: apatinib + TACE; NAT: non-Apatinib + TACE. For the rest of abbreviations see Fig. 2.

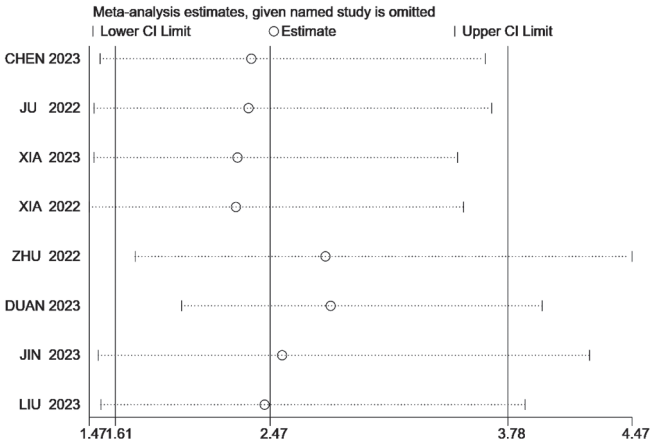

Fig. 7. Sensitivity analysis of the combined objective response rate.

treatment regimens in the control group: apatinib + TACE versus non-apatinib + TACE. The results indicated that different regimens in the control group were not the main source of heterogeneity (Fig. 6). Sensitivity analysis of the ORR was subsequently undertaken. In the sensitivity analysis, the joint results of ORR remained stable regardless of which study was removed, suggesting that the findings were relatively reliable (Fig. 7). The heterogeneity could be attributed to the different sample sizes of the studies, different types of PD-1 inhibitors, and various TACE regimens.

Publication Bias

The publication bias risk analysis of OS data was performed. The Egger's test (p=0.301) and the Begg's test (p=0.734) were employed to assess publication bias risk in OS data, in which no significant publication bias risk in OS data was found.

DISCUSSION

To our knowledge, this is the first and most comprehensive meta-analysis, addressing apatinib + TACE in combination with a PD-1 inhibitor for the treatment of HCC. In total, 8 studies [39-46] were included, accounting for enrollment of 2,352 patients with medium-to-advanced HCC. Importantly, all these studies were assessed as high-quality. The results revealed that the triple therapy group was effective in prolonging patients' OS (HR=0.42, 95%CI: 0.36-0.49) while yielding notably improved ORR (OR=2.47, 95%CI: 1.61-3.78) and DCR (OR=1.87, 95%CI: 1.44-2.44) compared with the non-triple therapy group.

Prior research has consistently identified HCC as a prototypical hypervascular tumor characterized by an abundance of tortuous blood vessels [47]. Hence, TACE stands as the standard treatment for intermediate-stage HCC [48-50]. However, a number of patients experience early recurrences following TACE [51-53]. Scholars have regarded adjuvant therapy post-TACE as a potential strategy to mitigate recurrence [54]. Previous research has indicated that apatinib in combination with TACE could significantly reduce tumor size, inhibit tumor hemodialysis, and prolong patient's survival

[55]. The 2022 Annual Meeting of the European Society for Medical Oncology in Asia (ESMO ASIA) reported the results of a study, in which patients in the TACE plus apatinib group had a median progression-free survival (PFS) of 6.83 months (95%CI: 4.53-10.15) [56]. Another phase III study demonstrated that treatment with TACE in combination with apatinib could significantly improve the median PFS of patients compared with the administration of TACE alone (17.2 vs. 12.5 months) [57]. In addition, studies have reported that the combination of antiangiogenic drugs with ICIs could lead to superior survival outcomes in HCC patients [33, 34]. Numerous fundamental studies have demonstrated that this effect arises from VEGF expression within tumors, which fosters an immunosuppressive microenvironment that promotes tumor growth by accumulating regulatory T cells, myeloid suppressor cells, immunosuppressive cytokines, inhibiting dendritic cell maturation and indoleamine 2,3-dioxygenase (IDO) production, suppressing T cell infiltration, and upregulating ICI expression in CD8+ T cells [58-62]. Therefore, it was attempted to clarify whether TACE + apatinib combined with a PD-1 inhibitor could further improve the prognosis of HCC patients. CHANCE001, a study conducted by the Chinese Liver Cancer Interventional Multidisciplinary Diagnosis and Treatment (MDT) Consortium, compared TACE plus immune and targeted agents with TACE alone. The results indicated that the median PFS in the combination therapy group was 9.5 months, which was significantly longer than that in the monotherapy group (8.0 months), while the median OS in the combination therapy group was 19.2 months versus 15.7 months for the monotherapy group [63].

Thus, TACE combined with TKIs and a PD-1 inhibitor can act synergistically to maximize HCC patients' prognosis, while AEs were not significantly affected [64].

This meta-analysis has some limitations. Firstly, the studies incorporated in this meta-analysis were retrospective in nature and featured relatively small sample sizes. Secondly, all of these studies were conducted in China, a region with a high prevalence of HCC, which may limit the generalizability of the findings to other populations. Thirdly, aspects, such as the selection of intra-arterial chemoembolization regimen, a specific PD-1 inhibitor employed, and the selection of these treatment regimens might be influenced by patients' physical and economic conditions, potentially introducing selection bias. Patients with greater hepatic function and economic conditions may have favored intra-arterial chemoembolization in conjunction with targeted and immunotherapy, while patients with poorer hepatic function and limited economic resources may have been inclined toward monotherapy. Fourthly, during the quality assessment, the NOS scoring was subjectively conducted by the investigators, which might enhance the risk of bias in the results. Finally, despite addressing the inherent data heterogeneity in the eligible studies, various other factors in the baseline characteristics of the studies, such as the number and size of tumors, the presence or absence of combined portal vein cancer emboli, and the general health status of the patients, were not consistently aligned across the trials, potentially confounding the conclusions.

In summary, TACE plus apatinib combined with a PD-1 inhibitor possesses the advantage of prolonging the survival of patients with advanced HCC compared with non-triple regimen therapies. However, further large-scale RCTs are required to validate the above-mentioned conclusions.

CONCLUSIONS

In this meta-analysis, the efficacy and safety of TACE + apatinib combined with a PD-1 inhibitor versus non-triple regimen therapies were compared. The results revealed that TACE + apatinib combined with a PD-1 inhibitor was superior to non-triple therapies for advanced primary HCC, and it was accompanied by a comparable safety profile. Thus, this study confirmed the applicability of this novel treatment for advanced primary HCC.

Conflicts of interest: None to declare.

Authors' contribution: Conception and design: Z.H., D.P., H.L., P.Q., X.C., X.M., Y.W., and X.Q conceived and designed the study. Z.H. was responsible for the administrative support. D.P., H.L., X.C., X.M., and Y.W. performed the literature search. D.P., H.L., X.M., P.Q., X.Q. collected and organized the data. H.L. analyzed and interpreted the data analysis. All the authors contributed to the draft and revisions of the manuscript. All the authors approved the final version of the manuscript.

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