BMC Cancer

SYSTEMATIC REVIEW

Open Access

PD-1 inhibitors improve the efficacy of transcatheter arterial chemoembolization combined with apatinib in advanced hepatocellular carcinoma: a meta-analysis and trial sequential analysis

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Abstract

Background The efficacy of adding programmed death-1 (PD-1) inhibitors to transcatheter arterial chemoembolization (TACE) combined with apatinib for advanced hepatocellular carcinoma (HCC) remains controversial. This study aimed to evaluate the efficacy of incorporating PD-1 inhibitors into TACE combined with apatinib.

Methods Relevant literature on TACE combined with apatinib plus PD-1 inhibitors for advanced HCC was searched in PubMed, Cochrane Library, Embase, and Web of Science databases. Trial sequential analysis (TSA) was conducted to minimize randomization errors and assess whether the meta-analysis provided conclusive evidence.

Results Six studies involving 1,452 patients were included. Compared with the TACE combined with apatinib treatment group (T-A), TACE combined with apatinib plus PD-1 inhibitors (T-A-P) significantly prolonged overall survival (OS) (Hazard Ratio [HR] 2.22, 95% Confidence Interval [CI] 1.93–2.56; $p < 0.001$) and progression-free survival (PFS) (HR 2.36, 95% CI 2.01–2.77; $p < 0.001$), while also improving the objective response rate (ORR) (risk ratios [RR] 1.60, 95% CI 1.20–2.14; $p < 0.001$) and disease control rate (DCR) (RR 1.06, 95% CI 1.00–1.12; $p < 0.001$). TSA results indicated that additional studies were required to confirm the significance of DCR. Prognostic analysis identified treatment regimen and extrahepatic metastasis as common independent risk factors for OS and PFS. The incidence of adverse events in the T-A-P treatment group was comparable to that in the T-A treatment group.

Conclusion Adding PD-1 inhibitors to TACE combined with apatinib significantly prolonged OS and PFS, particularly in patients without extrahepatic metastases. It also improved ORR and DCR in patients with HCC.

Keywords Transcatheter arterial chemoembolization, Apatinib, PD-1 inhibitors, Hepatocellular carcinoma, Meta-analysis, Trial sequential analysis

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant neoplasms globally, with China accounting for nearly half of the global patient population [1, 2]. This malignancy is characterized by a high mortality rate and poor patient prognosis, with the majority of patients diagnosed in the middle to late stages of the disease [3]. Approximately 70% of patients present with advanced-stage disease at the time of diagnosis, rendering surgical resection ineffective as a curative treatment. Consequently, local and systemic therapies have emerged as the predominant treatment modalities for advanced HCC. Local therapies primarily include transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy, and similar treatments, while systemic therapies comprise molecular targeted therapies and immune checkpoint inhibitors [4, 5].

TACE, a widely used treatment modality for HCC [6], primarily impedes tumor progression by occluding tumor blood vessels [7]. This approach has demonstrated notable short-term efficacy in patients with advanced HCC; however, its long-term effectiveness remains unsatisfactory. Prolonged ischemia and hypoxia lead to increased expression of vascular endothelial growth factor (VEGF), which in turn promotes tumor angiogenesis [8]. As a response to this adverse event, extensive research has focused on anti-angiogenic drugs, particularly tyrosine kinase inhibitors (TKIs). Apatinib, a TKI, exhibits high selectivity for vascular endothelial growth factor receptor-2, thereby inhibiting tumor vascularization [9]. A relevant study has indicated that TACE combined with apatinib is one of the commonly recommended treatment modalities for advanced HCC [10].

As a systemic treatment for HCC, programmed death-1 (PD-1) inhibitors have been shown to enhance the body's immune system by obstructing the PD-1 signaling pathway and consequently activating the immune response, thereby facilitating tumor cell elimination [11]. The therapeutic efficacy of TACE combined with apatinib has been demonstrated to surpass that of TACE alone, garnering significant clinical attention. Recently, relevant literature has shown that deep learning algorithms can be used to accurately identify tumor features and provide support for disease treatment decisions by mining the potential rules in complex medical data [12–14]. To provide evidence-based support for clinical decision-making, a comprehensive database search was conducted, including six related studies. The data from these studies were analyzed to assess the efficacy and safety of combining PD-1 inhibitors with TACE and apatinib. This treatment strategy has the limitations of high treatment cost and complex adverse drug reactions in clinical practice. However, this combination therapy can also change the thinking of clinical treatment options and improve the survival expectancy of eligible patients.

Methods

This systematic review and meta-analysis is registered on the PROSPERO website under registration number: CRD42025645599**,** and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [15].

Search strategy

A comprehensive search of the existing literature related to this study was conducted using the PubMed, Embase, Cochrane Library, and Web of Science databases, including all literature published up to January 14, 2025. The primary keywords used in the search strategy included "transcatheter arterial chemoembolization," "TACE," "programmed death-1 inhibitors," "PD-1," "PD-1 inhibitors," "pembrolizumab," "camrelizumab," "sintilimab," and "apatinib." No language restrictions were applied during the search process. The detailed search strategy employed for this article is outlined in Table S1.

Eligibility criteria

Studies were included if they met the following criteria: (1) patients diagnosed with Barcelona Clinic Liver Cancer (BCLC) stage B or C; (2) Child -Pugh class A or B; (3) clinically confirmed unresectable HCC; (4) treatment with TACE in combination with apatinib, with or without PD-1 inhibitors; (5) age $\geq$ 18 years; and (6) outcome measures including survival endpoints such as overall survival (OS), progression—free survival (PFS), along with response metrics like objective response rate (ORR) and disease control rate (DCR). Studies were excluded if they met any of the following criteria: (1) prior treatment with other therapies such as microwave ablation or radiofrequency ablation; (2) presence of concomitant malignancies in addition to HCC; (3) incomplete data or lack of follow-up; or (4) article types including reviews, letters, pathology reports, or studies without control groups.

Data extraction and quality assessment

The literature in the database was independently reviewed by two authors, who extracted the required data using a tabular format. After completing the data extraction process, the two authors summarized the extracted data. In cases where discrepancies arose, the data was meticulously re-examined by both authors. If consensus could not be reached, a third author was consulted to resolve the discrepancies and finalize the data extraction and summary. The raw data extracted for this meta-analysis primarily included study characteristics,

such as the first author's name, year of publication, and type of experimental design; basic patient characteristics, including gender, age, alpha-fetoprotein levels, tumor size, Child–Pugh class, and BCLC stage; and outcome indicators, including OS, PFS, ORR, and DCR. For studies using propensity score matching (PSM), data were extracted both before and after PSM analysis.

The quality of the included studies was independently evaluated by two authors using the Newcastle–Ottawa Scale (NOS). The NOS assesses study quality across three domains: selection of the study population, comparability, and exposure or outcome evaluation. Each section is rated using a semi-quantitative star system, with a total of eight entries. With the exception of the "Comparability" category, which is capped at two stars, the remaining entries are assigned a maximum of one star, with a total possible score of nine stars. A higher score indicates higher study quality. In this context, studies scoring between five and nine are considered high quality, while those scoring below five are classified as low quality [16].

Statistical analysis

For continuous variables such as OS and PFS, hazard ratios (HRs) and 95% confidence intervals (CIs) were used to report survival outcomes. For dichotomous variables such as ORR and DCR, risk ratios (RRs) and 95% CIs were used to report survival outcomes. The analysis was conducted using Review Manager 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark), Stata/MP version 17.0 (STATA Corp, College Station, TX, USA), and GraphPad Prism 9.5.1 (GraphPad Software, San Diego, CA, USA). A statistically significant difference was indicated when the p—value was less than 0.05. The heterogeneity of the included studies was assessed using the Q-test and I^2-test, where $I^2 > 50\%$ and $P < 0.05$ were considered indicators of high heterogeneity. In cases of high heterogeneity, a sensitivity analysis was performed to evaluate the stability of the findings. Regardless of the level of heterogeneity, a random -effects model was applied for data analysis. Egger's test and Begg's test were employed to assess publication bias. The modified Response Evaluation Criteria in Solid Tumors was used to evaluate tumor response in this study [17].

To further validate the final results, individual patient data (IPD) reconstruction was performed. First, the Kaplan–Meier survival curves from the six included studies were extracted, with separate extraction of survival graphs for OS and PFS. The IPD data was then reconstructed using the extraction method proposed by Liu et al. [18]. By tracing the survival curves individually, the raw survival time and status data were obtained, allowing for the construction of the final IPD model. For studies that reported Kaplan–Meier survival curves before and after PSM analysis, the data was extracted separately for both pre- and post-PSM analysis.

Meta-regression analysis

Meta-regression analysis was conducted to evaluate the effects of specific factors, including sample size and treatment strategy, on the study results. Sample size and treatment strategy were used as independent variables, while OS and PFS served as dependent variables. The grouping criteria were defined as follows: sample size (>100 vs. ≤ 100 patients) and treatment strategy (TACE + apatinib + PD-1 inhibitors vs. TACE + apatinib + camrelizumab).

Trial sequential analysis

Trial sequential analysis (TSA) is a statistical method based on cumulative evidence that updates and integrates information throughout the course of a study to assess the effectiveness of an intervention at an earlier stage. This is achieved by calculating the required information size (RIS), hypothesis testing boundaries, and null lines, among other parameters. TSA is effective in controlling Type I and Type II errors, reducing the likelihood of false-positive results caused by random errors. Termination signals for clinical trials are provided by calculating the RIS [19]. In this study, the RIS was calculated with a 5% risk of Type I error and 80% statistical power. Based on previous clinical experience, dichotomous outcome indicators such as ORR and DCR were analyzed using a relative risk reduction of 30%, while continuous outcome indicators such as OS and PFS were calculated using empirical mean deviation and variance to determine the RIS. The TSA analysis made use of TSA 0.9.5.10 Beta for its conduction (http://www.ctu.dk/tsa/).

Results

Study selection

A total of 123 relevant studies were identified during the initial database search. After removing 53 duplicate records, the remaining studies were screened based on titles and abstracts, leading to the exclusion of 25 additional papers. Simultaneously, 39 case reports, reviews, and meta-analyses were excluded. After multiple rounds of screening, the full texts of six studies were thoroughly reviewed, and these six studies were ultimately included in the meta-analysis [20–25]. The detailed study selection process is illustrated in Figure S1.

Study characteristics

Table 1 provides an overview of the fundamental characteristics of the six studies included in this meta-analysis. These studies were published between 2022 and 2024,

Table 1 Baseline characteristics of all included studies

study	year	treatment strategy	NO. of patients	age (mean/median)	male/female	AFP	study design	tumor size (cm)	Child–Pugh class(A/B)	BCLC stage(B/C)	ECOG PS (0/1)
Duan	2023	T + A + C	483	52.6 ± 9.2	399/84	≤ 400/ > 400:198/285	RCS	11.89 ± 5.06	193/290	85/398	283/200
		T + A	477	52.9 ± 9.6	382/95	≤ 400/ > 400:162/315		12.39 ± 4.68	193/284	75/402	265/212
Liu	2023	T + A + C	37	< 60/ ≥ 60:25/12	32/5	< 400/ ≥ 400:20/17	RCS	< 5/ ≥ 5:15/22	32/5	19/18	27/10
		T + A	39	< 60/ ≥ 60:18/21	36/3	< 400/ ≥ 400:23/16		< 5/ ≥ 5:21/18	35/4	24/15	24/15
Wu[a]	2024	T + A + P	38	56.0 (51.8–63.8)	34/4	< 200/ ≥ 200:25/13	RCS	9.5 (6.9–11.0)	28/10	0/38	17/21
		T + A	52	54.0 (48.3–62.0)	43/9	< 200/ ≥ 200:28/24		8.8 (5.4–11.0)	43/9	0/52	18/34
Xia	2022	T + A + P	68	≤ 60/ > 60:49/19	62/6	< 400/ ≥ 400:42/26	RCS	7.01 ± 3.76	65/3	NA	13/55
		T + A	148	≤ 60/ > 60:98/50	126/22	< 400/ ≥ 400:87/61		7.71 ± 4.58	130/18	NA	21/127
Xia	2023	T + A + P	40	≤ 60/ > 60:29/11	36/4	< 400/ ≥ 400:25/15	RCS	7.32 ± 3.55	38/2	NA	10/30
		T + A	69	≤ 60/ > 60:47/22	61/8	< 400/ ≥ 400:34/35		7.23 ± 3.75	54/15	NA	15/54
Zhu	2022	T + A + C	34	< 60/ ≥ 60:23/11	29/5	< 200/ ≥ 200:21/13	RCS	< 10/ ≥ 10:27/7	30/4	13/21	19/15
		T + A	114	< 60/ ≥ 60:65/48	84/29	< 200/ ≥ 200:67/46		< 10/ ≥ 10:85/28	105/18	73/40	62/51

Abbreviations: *RCS* Retrospective cohort studies, *T* Transcatheter arterial chemoembolization, *A* Apatinib, *C* Camrelizumab, *P* Programmed cell death-1 inhibitor, *AFP* Alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

[a] The data are presented as longest diameter of liver tumor (median, Q1, Q3)

Table 2 Baseline characteristics of all included studies after PSM analysis

study	year	treatment strategy	NO. of patients	age (mean/median)	male/female	AFP	study design	tumor size (cm)	Child–Pugh class(A/B)	BCLC stage(B/C)	ECOG PS (0/1)
Duan	2023	T + A + C	449	52.7 ± 8.9	372/77	≤ 400/ > 400:168/281	RCS	11.91 ± 4.95	175/274	78/371	262/187
		T + A	449	52.7 ± 9.1	367/82	≤ 400/ > 400:162/287		12.27 ± 4.57	185/264	75/374	256/193
Xia	2022	T + A + P	59	≤ 60/ > 60:41/18	53/6	< 400/ ≥ 400:35/24	RCS	6.85 ± 3.77	56/3	NA	12/47
		T + A	59	≤ 60/ > 60:43/16	54/5	< 400/ ≥ 400:32/27		6.94 ± 4.46	57/2	NA	12/47
Xia	2023	T + A + P	28	≤ 60/ > 60:20/8	25/3	< 400/ ≥ 400:16/12	RCS	6.95 ± 3.35	26/2	NA	7/21
		T + A	28	≤ 60/ > 60:19/9	26/2	< 400/ ≥ 400:17/11		7.51 ± 3.43	26/2	NA	7/21
Zhu	2022	T + A + C	34	< 60/ ≥ 60:23/11	29/5	< 200/ ≥ 200:21/13	RCS	< 10/ ≥ 10:27/7	30/4	13/21	19/15
		T + A	68	< 60/ ≥ 60:41/27	58/10	< 200/ ≥ 200:35/33		< 10/ ≥ 10:47/21	56/12	26/42	34/34

Abbreviations: RCS Retrospective cohort studies, *T* Transcatheter arterial chemoembolization, *A* Apatinib, *C* Camrelizumab, *P* Programmed cell death-1 inhibitor, *AFP* Alpha-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

and all were retrospective cohort studies. A total of 1,452 patients with HCC were included in the analysis, with 667 patients receiving TACE combined with apatinib plus PD-1 inhibitors and 785 patients receiving TACE combined with apatinib alone.

Four of the six included studies incorporated PSM analysis, and Table 2 summarizes the baseline characteristics of these four studies. Among the 1,174 patients with HCC analyzed in these studies, 570 patients were in the TACE combined with apatinib plus PD-1 inhibitors group, while 604 patients were in the TACE combined with apatinib treatment group.

Regarding the choice of PD-1 inhibitors, three of the included studies used camrelizumab alone [20, 21, 25], while the remaining three studies included camrelizumab, sintilimab, pembrolizumab, atezolizumab, and tislelizumab as PD-1 inhibitors [22–24].

Quality assessment

NOS was used for quality assessment, with the scoring rules for star ratings strictly followed. Since four of the included studies applied PSM analysis, multiple confounding factors were carefully controlled, ensuring comparability between cohorts. These studies received the highest NOS score of 9 [20, 23–25]. One study received a score of 7 due to the absence of follow-up data [22]. while the remaining study received a score of 8. Notably, all included studies scored above 5, indicating high methodological quality. The specific quality assessment results are detailed in Table S2.

Clinical outcomes

Overall survival

Prior to PSM analysis, OS-related data were reported in all included studies except for the study by Zhu et al. [25], which did not report OS. The results indicated that the TACE combined with apatinib plus PD-1 inhibitors (T-A-P) triple therapy group demonstrated a significant improvement in OS (HR 2.22, 95% CI: 1.93–2.56; $p < 0.001$) in patients with HCC compared to the TACE combined with apatinib (T-A) duo therapy group, with no evidence of significant heterogeneity ($I^2 = 0.00\%$; $p = 0.997$) (Fig. 1). Further analysis of the four studies that incorporated PSM analysis confirmed that the T-A-P triple therapy group significantly improved OS in patients with HCC (HR 2.29, 95% CI: 1.95–2.68; $p < 0.001$) compared to the T-A duo therapy group, again without significant heterogeneity ($I^2 = 0.00\%$; $p = 0.746$) (Figure S2).

Progression-free survival

Before PSM analysis, PFS-related data were reported in all included studies except for the study by Zhu et al. [25], which did not report PFS. The findings indicated that the T-A-P triple therapy group exhibited a substantial improvement in PFS (HR 2.36, 95% CI: 2.01–2.77; $p < 0.001$), with low heterogeneity ($I^2 = 22.9\%$; $p = 0.268$) compared to the T-A duo therapy group (Fig. 1). Further analysis of the four studies that underwent PSM analysis showed that the T-A-P triple therapy group significantly increased PFS in patients with HCC compared to the T-A duo therapy group (HR 2.61, 95% CI: 2.31–2.95; $p < 0.001$), with no significant heterogeneity ($I^2 = 0.00\%$; $p = 0.960$) (Figure S2).

Objective response rate and disease control rate

All included studies reported ORR-related data except for the study by Zhu et al., which did not report ORR [25]. The findings demonstrated that the T-A-P triple therapy group achieved a significant improvement in ORR (RR 1.60, 95% CI: 1.20–2.14; $p < 0.001$), though with substantial heterogeneity ($I^2 = 71.2\%$; $p = 0.008$) compared to the T-A duo therapy group (Fig. 2).

DCR-related data were reported in all included studies except for the study by Zhu et al., which did not report DCR [25]. The results showed that the T-A-P triple therapy group significantly improved DCR (RR 1.06, 95% CI: 1.00–1.12; $p < 0.001$), with low heterogeneity ($I^2 = 5.9\%$; $p = 0.373$) compared to the T-A duo therapy group (Fig. 2).

Prognostic factor analysis

Independent prognostic factors for OS and PFS were analyzed, revealing that treatment option (T-A-P vs. T-A), tumor size (< 5 cm vs. ≥ 5 cm), alpha-fetoprotein level (< 400 vs. ≥ 400 ng/mL), total bilirubin level, and extrahepatic metastasis (yes/no) were independent risk factors for OS. Similarly, treatment option (T-A-P vs. T-A), sex (male vs. female), Eastern Cooperative Oncology Group performance status score (0 vs. 1), and extrahepatic metastasis (yes/no) were identified as independent prognostic factors for PFS. The specific results of this analysis are detailed in Table 3.

Adverse events

Adverse events (AEs) were reported in all included studies. The findings demonstrated that for all-grade AEs, the incidence in the T-A-P treatment group was comparable to that in the T-A treatment group (RR 1.17, 95% CI: 1.12–1.22; p < 0.001), with high heterogeneity ($I^2 = 65.4\%$; $p < 0.001$) and a statistically significant difference between the groups. In the case of grade 3/4 AEs, the incidence in the T-A-P treatment group was also comparable to that in the T-A treatment group (RR 1.15, 95% CI: 0.96–1.38; $p = 0.125$), with no significant heterogeneity ($I^2 = 0.00\%$; $p = 0.863$) and no statistically significant difference between the groups.

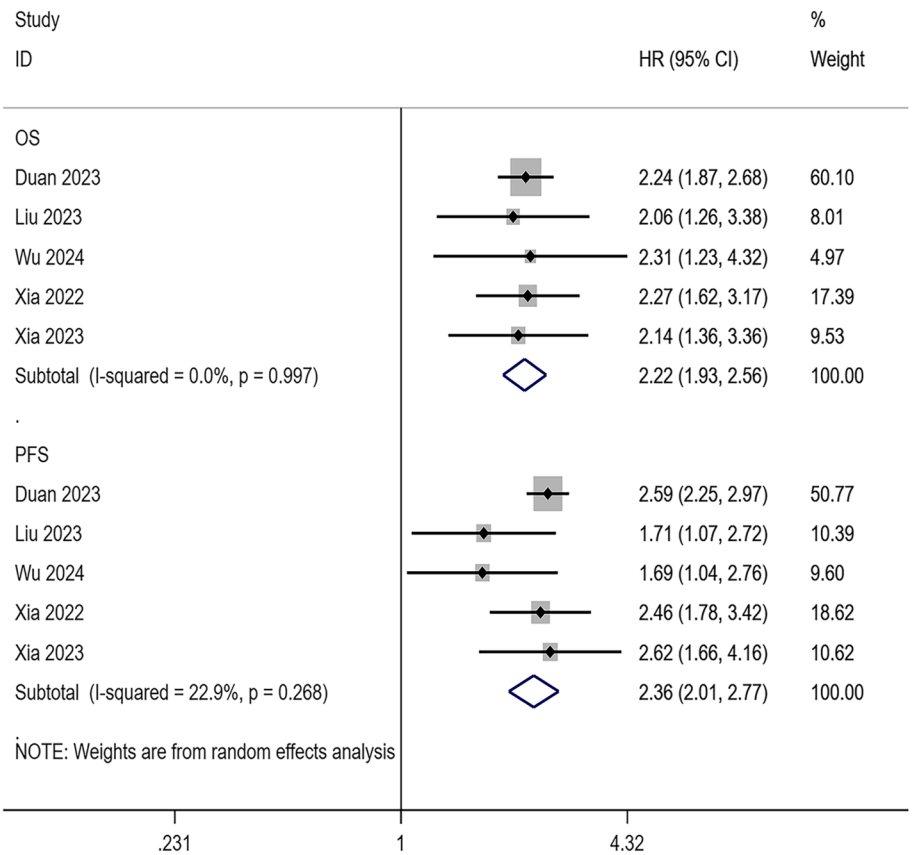

Fig. 1 Forest plots for the comparison of overall survival (OS) and progression free survival (PFS). CI, confidence interval; HR, hazard ratio

A detailed analysis of various adverse events was conducted, with the specific results presented in Table S3. Among all-grade AEs, decreased appetite, proteinuria, hoarseness, gastrointestinal hemorrhage, and hand-foot syndrome were frequently observed in patients with HCC treated with TACE in combination with apatinib. Thrombocytopenia, rash, and other adverse events were also commonly reported; however, these findings did not reach statistical significance. Among grade 3/4 AEs, fatigue, diarrhea, proteinuria, and hypertension were frequently observed in patients treated with TACE in combination with apatinib, though these findings also lacked statistical significance.

IPD reconstruction

We compared the overall Kaplan–Meier (KM) survival curves for OS and PFS between the T-A-P and T-A treatment groups by performing survival analysis on the raw data generated after tracing the individual data points. The results showed that the T-A-P treatment group significantly prolonged OS (median: 23.61 vs. 15.08 months, $p < 0.001$) (Fig. 3A) and PFS (median: 9.97 vs. 6.51 months, $p < 0.001$) (Fig. 3B) compared to the T-A treatment group.The PSM-adjusted KM survival curve analysis further confirmed that the T-A-P treatment group significantly improved OS (median: 24.35 vs. 16.34 months, $p < 0.001$) (Fig. 3C) and PFS (median: 10.38 vs. 6.99 months, $p < 0.001$) (Fig. 3D) compared to the T-A treatment group.

Meta-regression

To assess the potential influence of specific factors, including sample size and treatment strategy, on OS and PFS outcomes, we performed a meta-regression analysis, with the specific results presented in Table S4. The results indicated that sample size was not significantly associated with OS (coefficient: −0.04, 95% CI: −0.71 to 0.64, $p = 0.874$) or PFS (coefficient: −0.41, 95% CI: −0.99 to 0.17, $p = 0.109$). Similarly, treatment strategy did not significantly impact OS (coefficient: 0.01, 95% CI: −0.48 to 0.49, $p = 0.966$) or PFS (coefficient: −0.02, 95% CI: −0.69 to 0.65, $p = 0.926$). Therefore,

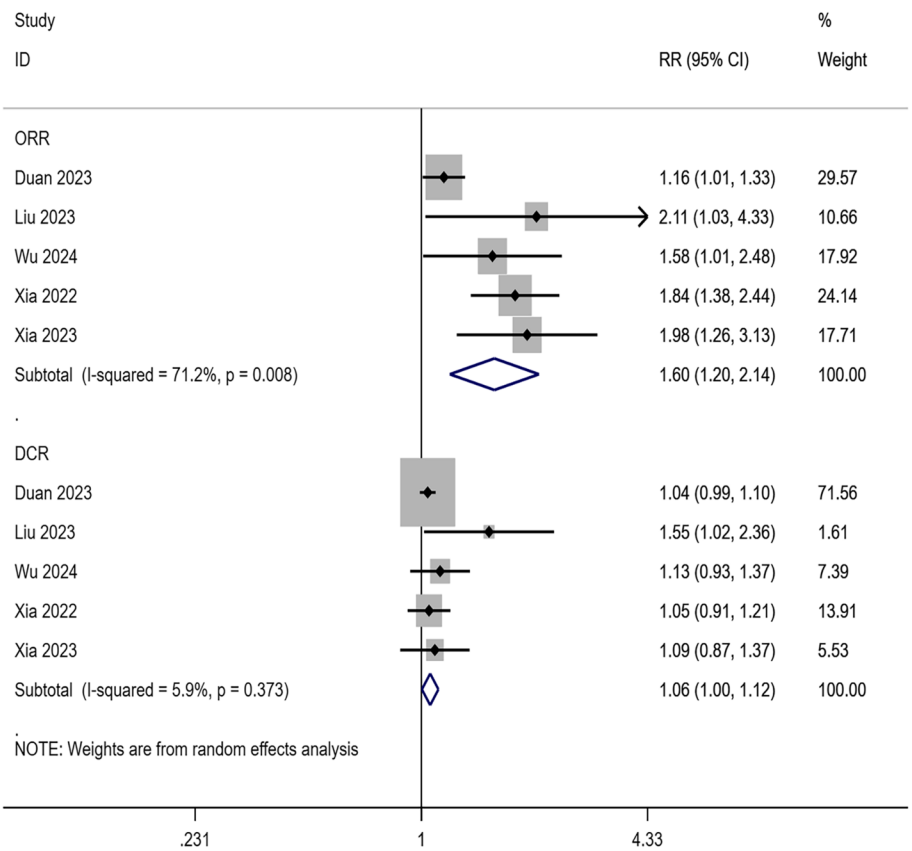

Fig. 2 Forest plots for the comparison of the objective response rate (ORR) and disease control rate (DCR). CI, confidence interval; RR, risk ratio

Table 3 Analyses of prognostic factors for survival of OS and PFS

	OS		PFS	
	HR(95%CI)	*P*	HR(95%CI)	*P*
Treatment option	0.41(0.35,0.48)	< 0.001	0.39(0.34,0.44)	< 0.001
Tumor size	1.28(1.07,1.54)	0.008	1.60(0.98,2.63)	0.062
BCLC stage	1.28(1.03,1.60)	0.030	-	-
AFP level	1.61(1.18,2.18)	0.002	-	-
Sex	2.57(0.98,6.73)	0.056	2.15(1.01,4.58)	0.046
ECOG PS score	-	-	1.15(1.01,1.30)	0.039
TBIL	1.03(1.01,1.06)	0.005	-	-
Extrahepatic metastasis	2.62(1.33,5.11)	0.005	2.47(1.40,4.36)	0.002

Abbreviation: OS Overall survival, *PFS* Progression free survival, *HR* Hazard ratio, *BCLC* Barcelona clinic liver cancer, *TBIL* Total bilirubin, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

neither sample size nor treatment strategy were identified as significant influencing factors for OS or PFS.

Trial sequential analysis

Figure S3 presents the results of TSA for OS and PFS. For OS, the TSA results showed that the RIS for the meta-analysis was 235, and the cumulative z-value crossed both the traditional and TSA monitoring boundaries, as well as the required information threshold. This indicates that the T-A-P treatment group significantly improved OS in patients with HCC compared to the T-A treatment group, providing conclusive evidence (Figure S3A). Similarly, for PFS, the TSA results demonstrated that the required sample size for the meta-analysis was 275, and the cumulative z-value exceeded the traditional and TSA monitoring boundaries, confirming that the T-A-P treatment group significantly improved PFS in patients with HCC with conclusive evidence (Figure S3B).

Figure S4 illustrates the TSA results for ORR and DCR. For ORR, the TSA analysis showed that the required sample size for the meta-analysis was 2,595, and the cumulative z-value crossed both the traditional and TSA monitoring boundaries before reaching the expected information size. This indicates that a definitive conclusion had been obtained, demonstrating that the T-A-P treatment group significantly improved ORR in patients with HCC compared to the T-A treatment group (Figure S4A). However, for DCR, the TSA results indicated that

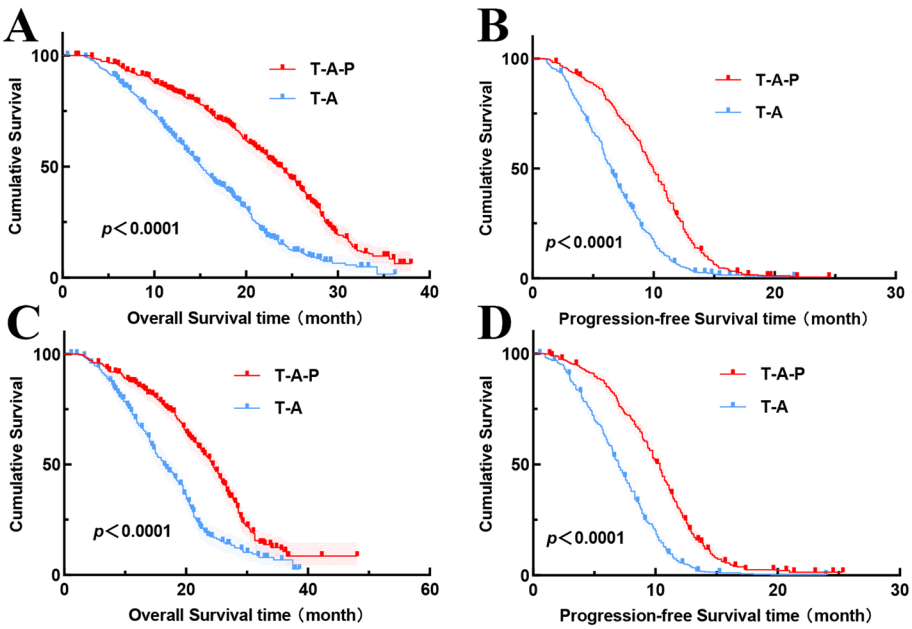

Fig. 3 A comparison of the combined survival curves for overall survival (**A**) and progression-free survival (**B**) in patients with HCC who were treated with T-A-P and T-A is presented. Additionally, the combined survival curves for overall survival (**C**) and progression-free survival (**D**) in patients with HCC who underwent a PSM analysis are shown. T-A-P, transcatheter arterial chemoembolization combined with apatinib plus PD-1 inhibitors; T-A, transcatheter arterial chemoembolization combined with apatinib

the required sample size for the meta-analysis was 605, and while the cumulative z-value crossed the traditional boundaries, it did not reach the TSA boundaries. This suggests that the conventional meta-analysis may have produced a false-positive result, and additional trials are needed to confirm the efficacy of the T-A-P treatment group in improving DCR (Figure S4B).

Sensitivity analysis and publication bias

We conducted a sensitivity analysis using the one-by-one elimination method, sequentially omitting one study at a time to assess the stability of the final results. Figure S5 presents the findings. The results demonstrated that for OS, the final outcomes remained stable (Figure S5A). However, for PFS, the results were not stable when the study by Duan et al. was omitted [20] (Figure S5B).

Publication bias was assessed using Egger's test and Begg's test, with the final results shown in Figure S6. For OS, the *p*-values from Egger's test and Begg's test were 0.501 and 0.462, respectively. For PFS, the *p*-values from Egger's test and Begg's test were 0.162 and 0.221, respectively. These results indicate that no publication bias was detected in the final analyses of OS and PFS.

Discussion

This meta-analysis was conducted to evaluate the efficacy and safety of TACE in combination with apatinib and PD-1 inhibitors in the treatment of advanced HCC compared to the T-A treatment group. The reliability of these findings was further validated through TSA. The TSA analysis indicated the potential for a false-positive conclusion in the DCR results, while OS, PFS, and ORR were confirmed as statistically robust. Regarding adverse events, the analysis of both all-grade and grade 3/4 AEs showed that the incidence of these events was higher in the T-A-P treatment group than in the T-A treatment group, with the observed differences being statistically significant. The prognostic factor analysis identified treatment option and extrahepatic metastasis as common independent risk factors for OS and PFS. Additionally, the meta-regression analysis demonstrated that sample size and treatment strategy were not significant influencing factors for OS and PFS. Furthermore, IPD reconstruction confirmed that the T-A-P treatment group significantly improved OS and PFS in patients with HCC compared to the T-A treatment group.

HCC is one of the most prevalent and lethal cancers worldwide [26]. Due to the complexity of the disease, an increasing number of therapeutic modalities have been explored for its treatment. A study has demonstrated that TACE in combination with apatinib can significantly improve clinical outcomes in patients with HCC [27]. Qin et al. conduct a randomized open-label trial comparing the combination of the PD-1 inhibitor camrelizumab and apatinib with sorafenib alone in advanced HCC. The results show that dual therapy with PD-1 inhibitor

camrelizumab combined with apatinib can significantly prolong OS and PFS of HCC patients compared with sorafenib alone, and further consolidate the efficacy of dual therapy for advanced HCC [28]. While dual therapy has been shown to enhance survival, its efficacy remains inferior to that of triple therapy, which is emerging as a more promising treatment option. A systematic review and meta-analysis is conducted to compare the efficacy of triple combination therapy TACE in combination with apatinib plus PD-1 inhibitor to non-triple combination therapy in advanced hepatocellular carcinoma. The non-triple combination therapy includes: TACE in combination with apatinib, PD-1 inhibitor in combination with apatinib, and TACE treatment alone. The findings of the study indicate that the triple combination therapy significantly prolongs the survival time of patients when compared to the non-triple combination therapy [29]. This finding serves to reinforce the efficacy of triple therapy in the treatment of advanced hepatocellular carcinoma. This meta-analysis focuses on evaluating the efficacy and safety of adding PD-1 inhibitors to TACE combined with apatinib.

The findings of our meta-analysis demonstrated that TACE combined with apatinib plus PD-1 inhibitors significantly prolonged survival in HCC patients. Our IPD reconstruction analysis estimated a median overall survival (mOS) of 23.61 months and a median progression-free survival (mPFS) of 9.97 months. A retrospective study assessing the efficacy of TACE in combination with apatinib plus PD-1 inhibitors reported a similar mOS of 24.5 months and an mPFS of 10.8 months [20],corroborating our findings. Additionally, other studies have confirmed the efficacy of combining TACE with targeted therapy and immunotherapy in advanced HCC [30, 31]. The mechanism underlying the improved survival associated with this combination therapy can be attributed to several factors. First, following TACE treatment, tumor cells may induce neovascularization by activating angiogenic factors such as VEGF, increasing the risk of tumor recurrence. Apatinib effectively inhibits VEGF-mediated angiogenesis, thereby reducing the likelihood of tumor recurrence after TACE treatment [32]. Second, the local inflammatory response triggered by TACE attracts immune cells to the tumor microenvironment, where PD-1 inhibitors enhance their activity, improving tumor cell recognition and elimination. This effect extends beyond local tumor cells and may also impact distant metastatic lesions [11, 33]. Finally, apatinib enhances the tumor microenvironment by inhibiting angiogenesis and modulating immune cell function, thereby facilitating immune cell infiltration and activity within tumor tissues. PD-1 inhibitors further activate T cells, and together, they work synergistically to overcome tumor immune evasion and enhance the body's anti-tumor immune response [34].

The findings of this study demonstrated that the combination of TACE with apatinib and PD-1 inhibitors resulted in a mOS of 23.61 months and a mPFS of 9.97 months. However, we observed that the mOS and mPFS reported in the study by Liu et al. were 15.4 months and 7.4 months, respectively [21]. The survival duration in that study was considerably shorter than that observed in our analysis. Conversely, the study by Duan et al. reported an mOS of 24.5 months and an mPFS of 10.8 months, which closely aligns with our findings. A comparative analysis of patient characteristics in these two studies revealed that the percentage of extrahepatic metastasis was 20.9% in Liu et al. and 43.2% in Duan et al., while the proportion of patients with multiple tumors was 58% and 83.8%, respectively. The higher tumor burden observed in the latter study suggests that increased tumor load may have influenced survival outcomes [20, 21]. Based on these findings, we hypothesize that the lower survival times reported by Liu et al. could be attributed to a higher incidence of extrahepatic metastasis and a greater tumor burden [21]. The results of our sensitivity analysis further indicated that the final outcomes were not stable when the study by Duan et al. was omitted [20]. This instability can be attributed to the relatively small number of included studies, the substantial variation in sample sizes, and the disproportionately large sample size of Duan et al., which accounted for more than 50% of the total sample size. As a result, this study carried significant weight and exerted a substantial influence on the overall pooled results. Consequently, when the study by Duan et al. was excluded, the overall results were rendered unstable [20].

Our prognostic factor analysis identified extrahepatic metastasis as a common independent risk factor for OS and PFS, a finding that aligns with previous related studies [35, 36]. A prior study evaluating the efficacy of TACE combined with targeted therapy and immunotherapy in advanced hepatocellular carcinoma used subgroup analysis to compare treatment outcomes. The results indicated that this triple therapy regimen was less effective in patients with extrahepatic metastases compared to those without [37]. These findings further support the conclusion that TACE combined with apatinib plus PD-1 inhibitors is more effective in patients without extrahepatic metastases.

The present study revealed that the study by Xia et al. reported an ORR of 63.2%, the highest among all included studies [23], whereas Liu et al. reported the lowest ORR at 43.2% [21]. To investigate the reason for this discrepancy, a comparative analysis of baseline characteristics was conducted. It was observed that the percentage

of patients with multiple tumors was 75% in Xia et al. and 83.8% in Liu et al. This suggests that the variation in ORR may be attributed to the increased tumor burden associated with a higher number of tumors. This finding is further supported by previous studies demonstrating that an increase in tumor load negatively impacts patient survival and response rates [38]. The results of our study showed that ORR and DCR were significantly improved in patients with HCC receiving the T-A-P treatment compared to the T-A treatment. A retrospective study evaluating the efficacy of TACE combined with sorafenib and PD-1 inhibitors demonstrated an increase in ORR from 34.5% to 54.6% and an increase in DCR from 55.17% to 81.82% [39]. Similarly, a retrospective study assessing TACE in combination with apatinib and camrelizumab in patients with unresectable HCC concluded that this regimen significantly improved ORR (58.8%) and DCR (81.2%) [40]. Their findings were consistent with those of the present study. However, TSA analysis suggested that the DCR outcome may have been a false-positive result. This is likely due to the inadequate sample sizes in the included studies, which limited the ability to reduce error and achieve a definitive conclusion. Therefore, future studies with larger sample sizes are needed to further validate DCR as a reliable outcome measure in this analysis.

Regarding the study's primary outcome—the occurrence of AEs—the results demonstrated that the incidence of AEs, including all -grade and grade 3/4 AEs, was comparable between the T-A-P and T-A treatment groups. This finding suggests that the addition of PD-1 inhibitors to the TACE regimen, in conjunction with apatinib, maintains an acceptable level of treatment tolerance. These observations are consistent with the conclusions of a previous meta-analysis [41]. However, no statistically significant differences were observed for grade 3/4 AEs. Several factors may account for this outcome: (1) Inadequate sample size, which may not accurately represent the overall patient population, leading to reduced statistical power and difficulty in detecting true associations between adverse events and treatment factors; (2) insufficient follow-up duration, which may have limited the ability to capture the occurrence or progression of adverse events. A longer follow-up period could introduce additional confounding variables, potentially affecting the study's precision. (3) poor adherence to study protocols, including non-compliance with medication regimens and missed follow-up visits, which may have further impacted the accuracy and reliability of the findings.

To identify potential influencing factors in this study, a meta-regression analysis was conducted to assess the impact of sample size and treatment strategy. The results indicated that neither factor significantly affected the findings, further confirming the stability of the study's conclusions. This study has several strengths. First, sample size adequacy was evaluated through TSA analysis, ensuring that false-positive results due to random errors were controlled. Moreover, TSA analysis preemptively suggested that the DCR outcome might be a false-positive, providing a basis for future investigations. Second, IPD reconstruction was performed to further validate the accuracy of our findings.

However, this study is not without limitations. First, all included studies were conducted in China, which may limit the generalizability of the findings to other populations. Second, the sample sizes of the included studies were relatively small, necessitating further expansion in future research. Third, The selection of PD-1 inhibitors presented in this literature constitutes a significant potential confounding factor. These inhibitors vary considerably in terms of their molecular structure, affinity for PD-1, binding sites, and pharmacokinetic profiles. However, a comparative analysis of the efficacy of various PD-1 inhibitors (nivolumab, pembrolizumab, sintilimab, tislelizumab, toripalimab, and camrelizumab) was conducted by Chen et al. using a reticulated meta-analysis approach. The results of this study indicated that, in clinical practice, the efficacy of these different PD-1 inhibitors was comparable, and all exhibited similar long-term survival effects [42]. However, it is acknowledged that further studies may be required in the future to account for this confounding factor. Forth, although four of the included studies reduced selection bias through PSM analysis [20, 23–25], selection bias remains inevitable given that all included studies were retrospective in nature. Given that all the studies included in this paper are retrospective, further validation is required through the conduct of large-scale, multicentre RCTs. Meta-analysis based on a certain number of RCTs may provide more reliable, evidence-based medical evidence for the combination of drugs in advanced hepatocellular carcinoma and the related guidelines to guide the clinical treatment. Finally, the stability of the results of the TSA analysis when the sample size is small will be challenged to accurately predict the amount of information required, which may lead to premature conclusions or delay the discovery of true effects. Conversely, the selection of model for TSA analysis exerts a substantial influence on the outcomes, with divergent model assumptions yielding disparate results.

Conclusion

In conclusion, this study provides preliminary evidence supporting the efficacy of TACE combined with apatinib plus PD-1 inhibitors in the treatment of advanced HCC,

particularly in patients without extrahepatic metastases. These findings establish a strong foundation for future research in this field.

Abbreviations

TACE	Transcatheter arterial chemoembolization
PD-1	Programmed death-1
HCC	Hepatocellular carcinoma
TSA	Trial sequential analysis
OS	Overall survival
PFS	Progression-free survival
ORR	Objective response rates
DCR	Disease control rates
AEs	Adverse events
CI	Confidence interval
HR	Hazard ratio
RR	Risk ratio
TKIs	Tyrosine kinase inhibitors
IPD	Individual patient data

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13932-4.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5: Figure S1.Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the process of identifying eligible studies.Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the process of identifying eligible studies.

Supplementary Material 6: Figure S2.Forest plot comparisons are employed to evaluate the comparative efficacy of overall survival (OS) and progression free survival (PFS) following PSM analysis. CI, confidence interval; HR, hazard ratio.

Supplementary Material 7: FigureS3.In the TSA analysis of the six included papers for the outcome indicators overall survival (OS) and progression free survival (PFS), the cumulative z-value exceeded both the conventional and TSA boundaries, and the cumulative information surpassed the anticipated information. A. With regard to OS, a RIS of 235 patients was calculated on the basis of an empirical MD and variance. B. For PFS, a RIS of 275 patients was calculated using an empirical MD and variance.

Supplementary Material 8: Figure S4. TSA analyses of the eight included papers for the outcome indicators ORR and DCR, A: With regard to objective response rate (ORR), the proportion of events occurring in the control group was 38.5%, the sample size required for the actual meta-analysis RIS was 2595, the cumulative z-value traversed both the conventional and TSA boundaries, and the cumulative information was more than the required amount of information. B: With regard to disease control rate (DCR), the proportion of events occurring in the control group was 79.5%. The sample size required for the actual meta-analysis is 605. The cumulative z-value did not traverse TSA boundaries. Furthermore, the cumulative information surpassed the anticipated information.

Supplementary Material 9: Figure S5.Sensitivity analysis plot based on (A) overall survival and (B) progression free survival.

Supplementary Material 10: Figure S6.The Egger's (A) and Begg's (B) test for OS; Egger's (C) and Begg's (D) test for PFS.

Acknowledgements
Not applicable.

Authors' contributions
All authors contributed to the conception and design of the study. Data were collected from J.X.Y and Y.C. Statistical analyses were performed using Y.Y and J.X.Y. Data interpretation was performed by J.H.Y and P.Y. J.H.Y and P.Y drafted and revised the manuscript. All the authors have read and approved the final version of the manuscript.

Funding
This study was supported by the Bureau of Science and Technology of Nanchong City (No. 22SXQT0052).

Data availability
The datasets generated are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 15 February 2025 Accepted: 12 March 2025
Published online: 28 March 2025

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