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Contents

Monthly Volume 16 Number 7 July 15, 2024

EDITORIAL

2867 Oncolytic virotherapy for hepatocellular carcinoma: A potent immunotherapeutic landscape

Xiao R, Jin H, Huang F, Huang B, Wang H, Wang YG

2877 Can the preoperative prognostic nutritional index be used as a postoperative predictor of gastric or gastroesophageal junction adenocarcinoma?

Feng YW, Wang HY, Lin Q

2881 Esophageal cancer: A global challenge requiring tailored strategies

Cheng CY, Hao WR, Cheng TH

2884 Effectiveness of transarterial chemoembolization in combination with lenvatinib and programmed cell death protein-1 inhibition for unresectable hepatocellular carcinoma

Chisthi MM

2888 Maximizing therapeutic outcomes in hepatocellular carcinoma: Insights into combinatorial strategies

Ilhan Y, Ergun Y

2894 Human β-defensin-1 activates autophagy in human colon cancer cells *via* regulation of long non-coding RNA TCONS_00014506

Eid N, Davamani F

REVIEW

2902 Role of molecular biology in the management of pancreatic cancer

Boileve A, Smolenschi C, Lambert A, Boige V, Tarabay A, Valery M, Fuerea A, Pudlarz T, Conroy T, Hollebecque A, Ducreux M

MINIREVIEWS

2915 Advances in immunotherapy of M2 macrophages and gastrointestinal stromal tumor

Wang XK, Yang X, Yao TH, Tao PX, Jia GJ, Sun DX, Yi L, Gu YH

ORIGINAL ARTICLE

Case Control Study

2925 Disparities in the diagnosis and treatment of colorectal cancer among patients with disabilities

Kim KB, Shin DW, Yeob KE, Kim SY, Han JH, Park SM, Park JH, Park JH

Retrospective Study

2941 Effectiveness and safety of sequential transarterial chemoembolization and microwave ablation for subphrenic hepatocellular carcinoma: A comprehensive evaluation

Zhu ZY, Qian Z, Qin ZQ, Xie B, Wei JZ, Yang PP, Yuan M

2952 Combined use of dexmedetomidine and nalbuphine in laparoscopic radical gastrectomy for gastric cancer

Zhao GG, Lou C, Gao RL, Lei FX, Zhao J

2960 Development and validation of a nomogram for predicting lymph node metastasis in early gastric cancer

He JY, Cao MX, Li EZ, Hu C, Zhang YQ, Zhang RL, Cheng XD, Xu ZY

Observational Study

2971 Comprehensive serum proteomics profiles and potential protein biomarkers for the early detection of advanced adenoma and colorectal cancer

Tan C, Qin G, Wang QQ, Li KM, Zhou YC, Yao SK

Clinical and Translational Research

2988 Network pharmacology- and molecular docking-based exploration of the molecular mechanism underlying Jianpi Yiwei Recipe treatment of gastric cancer

Chen P, Wu HY

2999 Survival disparities among racial groups with hepatic malignant tumors

Han D, Zhang ZY, Deng JY, Du HB

3011 Adipocytes impact on gastric cancer progression: Prognostic insights and molecular features

Shang JR, Zhu J, Bai L, Kulabiek D, Zhai XX, Zheng X, Qian J

3032 Integrated single-cell and bulk RNA sequencing revealed an epigenetic signature predicts prognosis and tumor microenvironment colorectal cancer heterogeneity

Liu HX, Feng J, Jiang JJ, Shen WJ, Zheng Y, Liu G, Gao XY

3055 Causal effects of genetic birth weight and gestational age on adult esophageal diseases: Mendelian randomization study

Ruan LC, Zhang Y, Su L, Zhu LX, Wang SL, Guo Q, Wan BG, Qiu SY, Hu S, Wei YP, Zheng QL

3069 Prognostic significance of exportin-5 in hepatocellular carcinoma

Li H, Li F, Wang BS, Zhu BL

3082 *BCAR3* and *BCAR3*-related competing endogenous RNA expression in hepatocellular carcinoma and their prognostic value

Shi HQ, Huang S, Ma XY, Tan ZJ, Luo R, Luo B, Zhang W, Shi L, Zhong XL, Lü MH, Chen X, Tang XW

3097 Glycolysis-related five-gene signature correlates with prognosis and immune infiltration in gastric cancer

Meng XY, Yang D, Zhang B, Zhang T, Zheng ZC, Zhao Y

Basic Study

3118 Kombo knife combined with sorafenib in liver cancer treatment: Efficacy and safety under immune function influence

Cao Y, Li PP, Qiao BL, Li QW

3158 Yiqi Jiedu Huayu decoction inhibits precancerous lesions of chronic atrophic gastritis by inhibiting NLRP3 inflammasome-mediated pyroptosis

Zhou P, Zheng ZH, Wan T, Liao CW, Wu J

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 7 July 15, 2024

Contents

3169 Multi-Omics analysis elucidates tumor microenvironment and intratumor microbes of angiogenesis subtypes in colon cancer

Yang Y, Qiu YT, Li WK, Cui ZL, Teng S, Wang YD, Wu J

3193 Baitouweng decoction suppresses growth of esophageal carcinoma cells through miR-495-3p/BUB1/STAT3 axis

Yang H, Chen XW, Song XJ, Du HY, Si FC

3211 Weiwei Decoction alleviates gastric intestinal metaplasia through the olfactomedin 4/nucleotide-binding oligomerization domain 1/caudal-type homeobox gene 2 signaling pathway

Zhou DS, Zhang WJ, Song SY, Hong XX, Yang WQ, Li JJ, Xu JQ, Kang JY, Cai TT, Xu YF, Guo SJ, Pan HF, Li HW

3230 Aldehyde dehydrogenase 2 family member repression promotes colorectal cancer progression by JNK/p38 MAPK pathways-mediated apoptosis and DNA damage

Yu M, Chen Q, Lu YP

3241 RBM5 suppresses proliferation, metastasis and glycolysis of colorectal cancer cells *via* stabilizing phosphatase and tensin homolog mRNA

Wang CX, Liu F, Wang Y

3256 Immune effect and prognosis of transcatheter arterial chemoembolization and tyrosine kinase inhibitors therapy in patients with hepatocellular carcinoma

Guo Y, Li RC, Xia WL, Yang X, Zhu WB, Li FT, Hu HT, Li HL

3270 N6-methyladenosine modification of hypoxia-inducible factor-1α regulates *Helicobacter pylori*-associated gastric cancer *via* the PI3K/AKT pathway

An TY, Hu QM, Ni P, Hua YQ, Wang D, Duan GC, Chen SY, Jia B

3284 Canopy FGF signaling regulator 3 affects prognosis, immune infiltration, and PI3K/AKT pathway in colon adenocarcinoma

Gao XC, Zhou BH, Ji ZX, Li Q, Liu HN

META-ANALYSIS

3299 Clinical and pathological features of advanced rectal cancer with submesenteric root lymph node metastasis: Meta-analysis

Wang Q, Zhu FX, Shi M

3308 Clinical benefits of transarterial chemoembolization combined with tyrosine kinase and immune checkpoint inhibitors for unresectable hepatocellular carcinoma

Han F, Wang XH, Xu CZ

SCIENTOMETRICS

3321 Research trends and hotspots in the immune microenvironment related to hepatocellular carcinoma: A bibliometric and visualization study

Zhang DY, Bai FH

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 7 July 15, 2024

Contents

CASE REPORT

3331 Gastric cancer metastatic to the breast: A case report

Liu JH, Dhamija G, Jiang Y, He D, Zhou XC

3341 Rare infiltrative primary hepatic angiosarcoma: A case report and review of literature

Lin XJ, Luo HC

3350 Metachronous multifocal carcinoma: A case report

Wan DD, Li XJ, Wang XR, Liu TX

3357 BRAF K601E-mutated metastatic colorectal cancer in response to combination therapy with encorafenib, binimetinib, and cetuximab: A case report

Sasaki M, Shimura T, Nishie H, Kuroyanagi K, Kanno T, Fukusada S, Sugimura N, Mizuno Y, Nukui T, Uno K, Kojima Y, Nishigaki R, Tanaka M, Ozeki K, Kubota E, Kataoka H

LETTER TO THE EDITOR

3364 Challenges in early detection and endoscopic resection of esophageal cancer: There is a long way to go

Liu S, Chen LX, Ye LS, Hu B

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 7 July 15, 2024

Contents

ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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META-ANALYSIS

Clinical benefits of transarterial chemoembolization combined with tyrosine kinase and immune checkpoint inhibitors for unresectable hepatocellular carcinoma

Feng Han, Xiao-Han Wang, Chen-Zhou Xu

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Abstract

BACKGROUND

Combination therapy has emerged as the focus of research for unresectable hepatocellular carcinoma (HCC). In recent years, several studies have explored the clinical efficacy and safety of the combination therapies of transarterial chemoembolization (TACE) with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs).

AIM

To conduct an updated meta-analysis verifying the clinical benefits and adverse effects of the triple combination therapy for unresectable HCC.

METHODS

All eligible cohort, non-randomized controlled, and randomized controlled trial studies from the PubMed, Web of Science, Embase, Cochrane Library, and MedLine databases up to March 20, 2024 were screened for the present meta-analysis. The study endpoints included complete response (CR), objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and adverse events (AEs). Stata 16/18 software was used for this meta-analysis, and a *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 29 studies with 1754 patients were included. Among the patients who received the TACE therapy with TKIs and ICIs, the tumor response results revealed a pooled CR, ORR, and DCR of 14% [95%CI (0.11–0.18)], 61% [95%CI (0.55–0.66)], and 85% [95%CI (0.83–0.87)], respectively. In terms of the survival outcomes, the pooled median PFS and OS were 10.25 months [95%CI (9.31–11.18)] and 20.47 months [95%CI (18.98–21.97)], respectively. The pooled prevalence of all-grade AEs during the triple treatment was 90% [95%CI (0.84–0.94)] and that of

grade ≥ 3 AEs was 32% [95%CI (0.24–0.42)].

CONCLUSION
The combination therapy of TACE, TKIs, and ICIs exhibits great clinical benefits for unresectable HCC in terms of tumor responses and survival outcomes without increasing the risk of severe AEs.

Key Words: Transarterial chemoembolization; Tyrosine kinase inhibitors; Immune checkpoint inhibitors; Hepatocellular carcinoma; Meta-analysis

Core Tip: Consensus regarding the treatment of unresectable hepatocellular carcinoma (HCC) currently remains lacking. The triple combination therapy of transarterial chemoembolization with tyrosine kinase and immune checkpoint inhibitors has attracted significant attention as an aggressive treatment strategy and has been used for treatment in recent years. We conducted a systematic review and updated meta-analysis to verify the clinical benefits and adverse effects of triple therapy in 29 studies with 1754 patients with unresectable HCC. The complete response, objective response rate, disease control rate, overall survival, progression-free survival, and adverse events induced by the triple therapy were evaluated.

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INTRODUCTION

Primary liver cancer is the most common and fatal solid malignancy worldwide[1]. In 2020, 905700 people were diagnosed with liver cancer, with 830200 fatalities globally[2]. The 5-year survival rate for liver cancer was 18% between 2006 and 2012[3]. The mortality rate of liver cancer increased by 43% from 2000 to 2016 in the United States[4]. By 2040, new cases and deaths from liver cancer may increase by > 55%[2]. Hepatocellular carcinoma (HCC) is the most common histological type of liver cancer, accounting for approximately 90% of cases[1]. Many curative treatments, including surgical resection, radiofrequency ablation, and liver transplantation, are available for patients with early HCC [Barcelona Clinic Liver Cancer (BCLC) 0 and A][5]. However, owing to the late presentation of symptoms, > 70% of patients are diagnosed with the intermediate (BCLC B) and advanced (BCLC C) HCC stages and mostly receive locoregional and systemic therapies[5-7].

Transarterial chemoembolization (TACE) is the most common and standard locoregional therapy in the management of patients with intermediate HCC[8]. TACE improved the survival outcomes of patients with unresectable HCC in random controlled trials conducted in Europe and Asia[5]. However, repeated TACE may impair liver function and even result in the development of TACE resistance. Consequently, TACE therapy alone is not sufficient for patients with advanced stages, especially portal vein invasion or extrahepatic spread[9,10]. Additionally TACE is generally not successful in controlling tumor progression because of the high incidence of incomplete embolization and embolization-related changes in the tumor microenvironment[11]. For systemic therapy, sorafenib, a multikinase inhibitor, was the first drug approved for the first-line systemic regimen. Treatment with sorafenib resulted in a longer median overall survival (OS) than the placebo group (10.7 *vs* 7.9 months) in patients with advanced HCC[12]. Lenvatinib is also an approved multikinase inhibitor for advanced HCC, and it demonstrated a comparable median OS of 13.6 *vs* 12.3 months for sorafenib in REFLECT trial[13]. Many other tyrosine kinase inhibitors (TKIs) and/or antiangiogenic VEGFR2 antagonists, such as regorafenib, cabozantinib, and ramucirumab, have shown significant improvements in the median OS of patients with HCC[14]. Immune checkpoint inhibitors (ICIs), including atezolizumab/bevacizumab, are also systemic first-line therapies for advanced HCC. Compared with sorafenib and lenvatinib, treatment with these ICIs resulted in the longest median OS of 15.03 months, median progression-free survival (PFS)of 7.97 months, and highest objective response rate (ORR) of 31.6%[15]. Recently, the combination of locoregional and systemic treatments has yielded impressive clinical outcomes[14]. A multicenter retrospective matched-cohort study of patients with HCC from 59 hospitals in China found that TACE combination therapy with PD-(L)1 inhibitors and molecular targeted agents significantly improved the median PFS, median OS, and ORR compared with TACE monotherapy[16]. A single-arm phase II trial based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) revealed that TACE plus lenvatinib and PD-1 inhibitors exhibited a high ORR of 60.0%, disease control rate (DCR) of 86.7%, long median OS of 18.4 months, and median PFS of 8.0 months, with 93.3% adverse events (AEs) of any grade, 40.0% grade 3 TRAEs, and no grade 4/5 TRAEs in patients with advanced HCC[17]. To date, numerous clinical trials and studies with or without control or intervention measures have explored the benefits of combination therapies of TACE with TKIs and ICIs using different treatment regimens and have achieved encouraging results.

Combination therapies with remarkable therapeutic potential have become the focus of research on unresectable HCC [6]. Survival outcomes, tumor responses, and adverse reactions caused by triple therapy have attracted much attention from academic researchers and scholars. Therefore, in this study, we conducted a meta-analysis to evaluate the clinical benefits and side effects of triple therapy of TACE combined with TKIs and ICIs in unresectable HCC using systematic and up-to-date data. Our study may serve as a reference for the selection of treatment regimens by clinicians.

MATERIALS AND METHODS

Search strategy and study selection

We identified the eligible studies from the PubMed, Web of Science, Embase, Cochrane Library, and MedLine databases up to March 20, 2024. The following terms were used: transarterial chemoembolization OR transcatheter arterial chemoembolization OR TACE AND tyrosine kinase inhibitors OR TKIs OR sorafenib OR lenvatinib AND immune checkpoint inhibitors OR ICIs OR programmed cell death protein 1 OR programmed cell death ligand 1 OR PD-1/L1 inhibitors OR atezolizumab OR bevacizumab AND liver cancer OR liver neoplasms OR hepatocellular carcinoma OR hepatocarcinoma OR HCC.

Inclusion and exclusion criteria

The inclusion criteria included: (1) Patients diagnosed with HCC; (2) Intervention using triple therapy of TACE with TKIs and ICIs; (3) No restriction on whether a control group or intervention was established; (4) Studies reporting at least one of the endpoints, such as complete response (CR), ORR, DCR, median PFS, median OS, all-grade AEs, and grade ≥ 3 AEs; and (5) Study design including cohort, non-randomized controlled, and randomized controlled trials. The exclusion criteria were as follows: (1) The use of monotherapy or combination therapies other than TACE with TKIs and ICIs; (2) Studies with insufficient data; (3) Studies that were not available; (4) Duplicate studies; and (5) Studies not reported in English.

Data extraction

The data were extracted by two professionals, and the following information was collected: (1) Characteristics of studies: first author's name, publication date, country, subjects, study design, treatment regimens, and sample size; (2) Characteristics of patients: median age, sex, whether hepatitis B virus-positive, α-fetoprotein levels, Child-Pugh grade, BCLC stage, extrahepatic metastasis, and portal vein tumor thrombus; (3) Endpoints reported in the articles: tumor responses (CR, ORR, and DCR), survival outcomes (median PFS and median OS), adverse effects (all-grade AEs and grade ≥ 3 AEs).

Statistical analysis

The tumor response was evaluated according to the mRECIST. ORR was defined as CR or partial response (PR), whereas DCR was defined as the sum of CR, PR, and stable disease. AEs and grade ≥ 3 AEs were evaluated based on the Common Terminology Criteria for Adverse Events. A meta-analysis of the pooled rates of CR, ORR, DCR, and AEs and the effect size of median PFS and OS with 95%CI was performed using Stata 16/18. The heterogeneity was evaluated using I^2 statistics, and $P > 0.10$ or $I^2 \geq 50\%$ was considered as apparent heterogeneity. A random-effect or fixed-effect model was used. $P < 0.05$ was considered statistically significant.

RESULTS

Study and patient characteristics

A flowchart of the study selection is illustrated in Figure 1. After excluding ineligible studies, 29 articles[17-45] with 1754 patients were included. Among the included studies, 27 were retrospective studies and 2 were prospective studies. In this meta-analysis, regardless of the presence or absence of control or intervention measures, patients who underwent triple combination therapy were included. The characteristics of the included studies and patients are presented in Table 1.

Tumor responses

Tumor responses are presented as forest plots in Figure 2. Tumor responses, including CR, ORR, and DCR, were reported in 21, 24, and 23 studies, respectively. The results revealed the pool CR rate (Figure 3A), ORR (Figure 3B), and DCR (Figure 3C) as 14% [95%CI (0.11–0.18)], 61% [95%CI (0.55–0.66)], and 85% [95%CI (0.83–0.87)], respectively. A random-effect model was used for CR ($I^2 = 50.98\%$; $P < 0.01$) and ORR ($I^2 = 70.47\%$; $P < 0.01$), and a fixed-effect model was used for DCR ($I^2 = 28.27\%$; $P = 0.10$).

Survival outcomes

Forest plots of survival outcomes are presented in Figure 3. In terms of survival outcomes, 22 and 16 studies reported PFS and OS data, respectively. The pooled results demonstrated that patients who underwent triple combination therapy exhibited a promising median PFS [10.25 months; 95%CI (9.31–11.18); Figure 2A]. Moreover, the triple therapy was associated with a long median OS [20.47 months; 95%CI (18.98–20.97); Figure 2B]. A random-effect model was employed because of the high I^2 values for the analysis of median PFS ($I^2 = 80.71\%$; $P < 0.01$) and OS ($I^2 = 73.59\%$; $P < 0.01$).

Table 1 Baseline characteristics of includes studies and patients

Ref.	Country	Subjects	Study design	Treatment regimen	Sample size	Age (yr)	Male (%)	Positive of HBV (%)	AFP < 400 ng/mL (%)	Child-Pugh A (%)	BCLC stage A/B/C	EHM (%)	PVTT (%)
Yuan *et al* [18], 2024	China	Patients with unresectable HCC	Retrospective	TACE + TKIs + ICIs	139	59 (50, 67)	121 (87.05)	115 (82.73)	103 (74.10)	119 (85.61)	0/99/40	23 (16.55)	31 (22.3)
Sun *et al* [19], 2024	China	Patients with advanced HCC	Retrospective	TACE + lenvatinib + sintilimab	40	55 ± 9	34 (85.0)	30 (75.0)	26 (65.0)	34 (85.0)	0/0/40	14 (35.0)	29 (72.5)
Sheng *et al* [20], 2024	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	113	64.48 ± 10.83	95 (84.1)	72 (63.7)	90 (79.6)	88 (77.9)	0/54/59	15 (13.3)	29 (25.7)
Cai *et al*[17], 2024	China	Patients with advanced HCC	Retrospective	TACE + lenvatinib + sintilimab	30	49.4 ± 9.9	26 (86.7)	25 (83.3)	NR	29 (96.7)	NR	13 (43.3)	NR
Gao *et al* [21], 2023	China	Patients with advanced HCC	Retrospective	TACE + TKIs + ICIs	41	52 (46, 57)	35 (85.4)	29 (70.7)	9 (22.0)	32 (78.0)	0/11/30	10 (24.4)	29 (70.7)
Li *et al*[22], 2023	China	Patients with advanced HCC	Prospective	TACE + TKIs + camrel-izumab	87	56 (34, 75)	81 (93.1)	75 (86.2)	51 (58.6)	51 (58.6)	NR/NR/69	43 (49.4)	65 (74.7)
Hu *et al*[44], 2023	China	Patients with unresectable HCC	Retrospective	TACE + TKIs + ICIs	98	52 (42, 62)	87 (88.8)	85 (86.7)	NR	75 (76.5)	0/12/86	49 (50.0)	14 (14.3)
Zhang *et al* [23], 2024	China	Patients with unresectable HCC	Retrospective	TACE + TKIs + ICIs	54	≤ 60: 38 (72.5); > 60: 16 (27.5)	46 (85.0)	53 (98.1)	26 (48.1)	54 (100)	0/23/31	19 (35.2)	NR
Wu *et al* [24], 2024	China	Patients with unresectable HCC	Prospective	TACE + lenvatinib + camrelizumab	55	54 (46, 62)	45 (81.8)	27 (49.1)	23 (41.8)	55 (100)	0//12/43	10 (18.2)	37 (67.3)
Gao *et al* [25], 2023	China	Patients with TACE-refractory HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	57	57.5 ± 9.4	45 (78.9)	43 (75.4)	NR	34 (59.6)	0/17/40	24 (42.1)	NR
Lu *et al*[26], 2023	China	Patients with unresectable HCC	Retrospective	TACE + donafenib + toripalimab	81	51.9±12.4	65 (80.2)	54(66.7)	NR	46 (56.8)	0/22/59	NR	NR
Pan *et al* [27], 2023	China	Patients with unresectable HCC	Retrospective	TACE + TKIs + ICIs	49	< 65: 38 (77.6); ≥ 65: 11 (22.4)	46 (93.9)	41 (83.7)	21 (42.9)	40 (81.6)	5/14/30	6 (12.2)	27 (55.1)
Wu *et al* [28], 2023	China	Patients with BCLC-defined stage C HCC	Retrospective	TACE + lenvatinib + camrelizumab	57	53.18 ± 9.25	49 (86.0)	44 (77.2)	25 (43.9)	52 (91.2)	0/0/57	23 (40.4)	NR
Wang *et al* [29], 2023	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	45	54 (18, 79)	42 (93.33)	42 (93.33)	13 (28.89)	NR	NR	18 (40.0)	20 (44.44)
Xin *et al*[30], 2023	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	60	57.5 (26, 76)	54 (90.0)	56 (93.4)	32 (53.3)	NR	0/21/39	18 (30.0)	28 (46.7)
Wang *et al* [31], 2023	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	46	55.54 ± 11.92	41 (89.1)	42 (91.3)	18 (39.1)	38 (82.6)	0/8/38	24 (52.2)	NR

Sun *et al* [32], 2023	China	Patients with advanced HCC	Retrospective	TACE + TKIs + camrel-izumab	70	53.8 ± 10.4	58 (82.9)	54 (77.1)	30 (42.9)	57 (81.4)	NR	NR	NR
Ju *et al*[33], 2021	China	Patients with unresectable HCC	Retrospective	TACE + apatinib + camrel-izumab	56	52 (26, 75)	46 (82.1)	48 (85.7)	NR	43 (76.8)	0/13/43	NR	NR
Cai *et al*[34], 2022	China	Patients with advanced HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	41	51.9 ± 10.3	37 (90.2)	35 (85.4)	20 (48.8)	37 (90.2)	NR	17 (41.5)	NR
Li *et al*[35], 2022	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	114	53 (24, 79)	102 (89.5)	102 (89.5)	NR	111 (97.4)	3/42/69	23 (20.2)	NR
Teng *et al* [36], 2022	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	53	56.9 (37, 75)	45 (84.9)	45 (84.9)	35 (66.0)	34 (64.2)	0/23/30	42 (79.2)	NR
Qu *et al*[37], 2022	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + PD-1 inhibitor	56	51 (24, 82)	51 (91.1)	43 (76.8)	34 (60.7)	53 (94.6)	0/17/39	29 (51.8)	NR
Yang *et al* [38], 2022	China	Patients with unresectable HCC	Retrospective	TACE + TKIs + ICIs	53	59 ± 10.6	45 (85.0)	47 (89.0)	34 (64.0)	34 (64.0)	2/29/22	NR	NR
Yang *et al* [39], 2021	China	Patients with unresectable HCC	Retrospective	TACE + TKIs + ICIs	31	57.5 ± 9.4	25 (80.6)	26 (83.9)	23 (74.2)	27 (87.1)	2/18/11	NR	NR
Liu *et al*[45], 2021	China	Patients with advanced HCC	Retrospective	TACE + lenvatinib + camrelizumab	22	57.7 ± 9.9	17 (77.3)	15 (68.2)	7 (31.2)	16 (72.7)	0/12/10	8 (36.4)	11 (50.0)
Wu *et al* [40], 2021	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + Anti-PD-1 antibodies	62	57 (23, 75)	56 (90.3)	57 (91.9)	30 (48.4)	62 (100.0)	6/21/35	6 (9.7)	15 (24.2)
Cao *et al* [41], 2021	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + sintilimab	52	≤ 65: 40 (76.9); > 65: 12 (23.1)	45 (86.4)	47 (90.4)	34 (65.4)	46 (88.5)	0/13/39	21 (40.4)	NR
Zheng *et al* [42], 2020	China	Patients with advanced TACE-refractory HCC	Retrospective	TACE + sorafenib + ICIs	22	< 55: 10 (45.45); ≥ 55: 12 (54.55)	19 (86.36)	17 (77.27)	7(31.82)	13 (59.03)	0/11/11	7(31.82)	7(31.82
Chen *et al* [43], 2022	China	Patients with unresectable HCC	Retrospective	TACE + lenvatinib + pembrolizumab	70	58 (36, 69)	37 (52.9)	38 (54.3)	25 (35.7)	70 (100.0)	0/47/23	NR	NR

HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; TKI: Tyrosine kinase inhibitor; ICI: Immune checkpoint inhibitor; HBV: Hepatitis B virus; AFP: α-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; EHM: Extrahepatic metastasis; PVTT: Portal vein tumor thrombosis.

AEs

Forest plots for AEs are presented in Figure 4. AEs mainly included hypertension, elevated alanine aminotransferase levels, fatigue, diarrhea, vomiting, decreased appetite, thrombocytopenia, and hypothyroidism. In this analysis, 18 studies reported all-grade AEs, and 13 studies reported grade ≥ 3 AEs. The pooled incidence of all-grade AEs was 90% [95%CI (0.84–0.94)] and that of grade ≥ 3 AEs was 32% [95%CI (0.24–0.42)]. A random-effect model was employed, and the I^2 values for all-grade AEs and grade ≥ 3 AEs were 84.16% ($P < 0.01$) and 83.51% ($P < 0.01$), respectively.

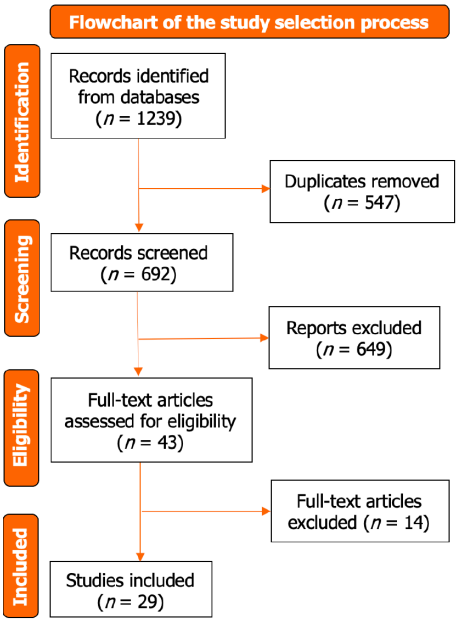


Figure 1 Flowchart of study selection.

DISCUSSION

Using locoregional therapy along with systemic therapy may be a promising choice for unresectable HCC. In this study, 29 studies with 1754 patients who underwent TACE therapy in combination with TKIs and ICIs were included, and the findings revealed an encouraging CR, ORR, DCR, OS, PFS, and acceptable AEs in patients with unresectable HCC.

The efficacy and safety of triple TACE therapy with TKIs and ICIs in patients with advanced HCC were first reported in 2021[45]. In that study, patients receiving TACE therapy with lenvatinib and camrelizumab exhibited an ORR of 72.7%, and the DCR reached 95.5% at the third month. Further, the median OS and PFS were 24 and 11.4 months, respectively, with no serious AEs or deaths[45]. Thereafter, numerous studies have explored the benefits of combination therapies using different treatment options. The superiority of the triple combination modality over TACE monotherapy, TACE + TKIs, and TKIs + ICIs has been demonstrated in many controlled studies. In 2020, the TACTICS trial compared the effectiveness of TACE and sorafenib with that of TACE monotherapy, and reported a significant improvement in PFS (25.2 *vs* 13.5 months; $P = 0.006$)[46]. Notably, the ORR of TACE plus lenvatinib treatment reached 88.7% for unresectable HCC in the TACTICS-L trial[47]. A propensity score matching retrospective study reported that the triple combination of TACE with TKIs and ICIs demonstrated better ORR (52.5% *vs* 32.8%; $P < 0.001$) and DCR (82.7% *vs* 59.6%; $P < 0.001$), and achieved longer OS (median OS, 21.9 *vs* 16.3 months; $P = 0.022$) and PFS (median PFS, 8.3 *vs* 5.1 months; $P < 0.0001$) than TACE alone, with AEs similar to those reported in previous TACE-related studies[18]. Single-agent ICIs have shown an ORR of 15%–20% in patients with advanced HCC, mostly with no significant benefit on OS, resulting in approximately 30% of HCCs exhibiting intrinsic resistance to ICIs[48]. Using a PD-1 inhibitor in addition to TACE and lenvatinib has shown significant improvements in efficiency and safety[20]. Compared with TACE with lenvatinib, TACE with lenvatinib and PD-1 inhibitor resulted in longer PFS (14.0 *vs* 9.0 months; $P < 0.001$) and OS (24.0 *vs* 15.0 months; $P < 0.001$), and a better overall ORR (54.0% *vs* 32.8%; $P = 0.001$), with no significant difference in the incidence of AEs (56.64% *vs* 46.09%; $P = 0.102$) and grade ≥ 3 AEs (11.50% *vs* 9.38%; $P = 0.588$)[20]. In 2022, the IMbrave150 trial demonstrated that atezolizumab with bevacizumab results in a higher OS than sorafenib (19.2 *vs* 13.4 months; $P < 0.001$) in patients with untreated HCC[49]. The OS of the TACE with TKI plus ICI group was significantly longer than that of the TKI plus ICI group (19.5 *vs* 10.8 months; $P = 0.005$), and major AEs were comparable in both groups (34.7% *vs* 30.6%; $P = 0.621$)[44].

The findings of the present study revealed that the triple combination therapy exhibited an encouraging pooled CR rate, ORR, and DCR of 14%, 61%, and 85%, respectively. Further, the pooled median PFS and OS were 10.25 and 20.47 months, respectively. Moreover, the pooled prevalence of all-grade AEs was 90%, and that of grade ≥ 3 AEs was 32%. Our data support the potential application of triple combination therapy for unresectable HCC, which may have great clinical benefits in tumor responses and survival outcomes without increasing the risk of severe AEs. The findings are consistent with a recent largest, multicenter, retrospective cohort study in China, which indicated that combining TACE with ICIs plus anti-VEGF antibody/TKIs can significantly improve the OS, PFS, and ORR, with an acceptable safety profile[50]. Additionally, two multicenter international study registered in the United States were conducted to evaluate TACE in combination with ICIs and lenvatinib therapy in patients with locoregional/incurable/non-metastatic HCC (NCT05301842, NCT04246177). The results of the two ongoing trials have been not posted yet, but we are looking forward to the improved clinical effects of the triple therapy for HCC. Table 2 presents the ongoing clinical trials exploring the clinical benefits of the triple combination modality.

This study has some limitations. First, the retrospective design of the most included studies may have caused recall bias in this study. Second, conducting the subgroup analysis was difficult because of the small sample size of all included

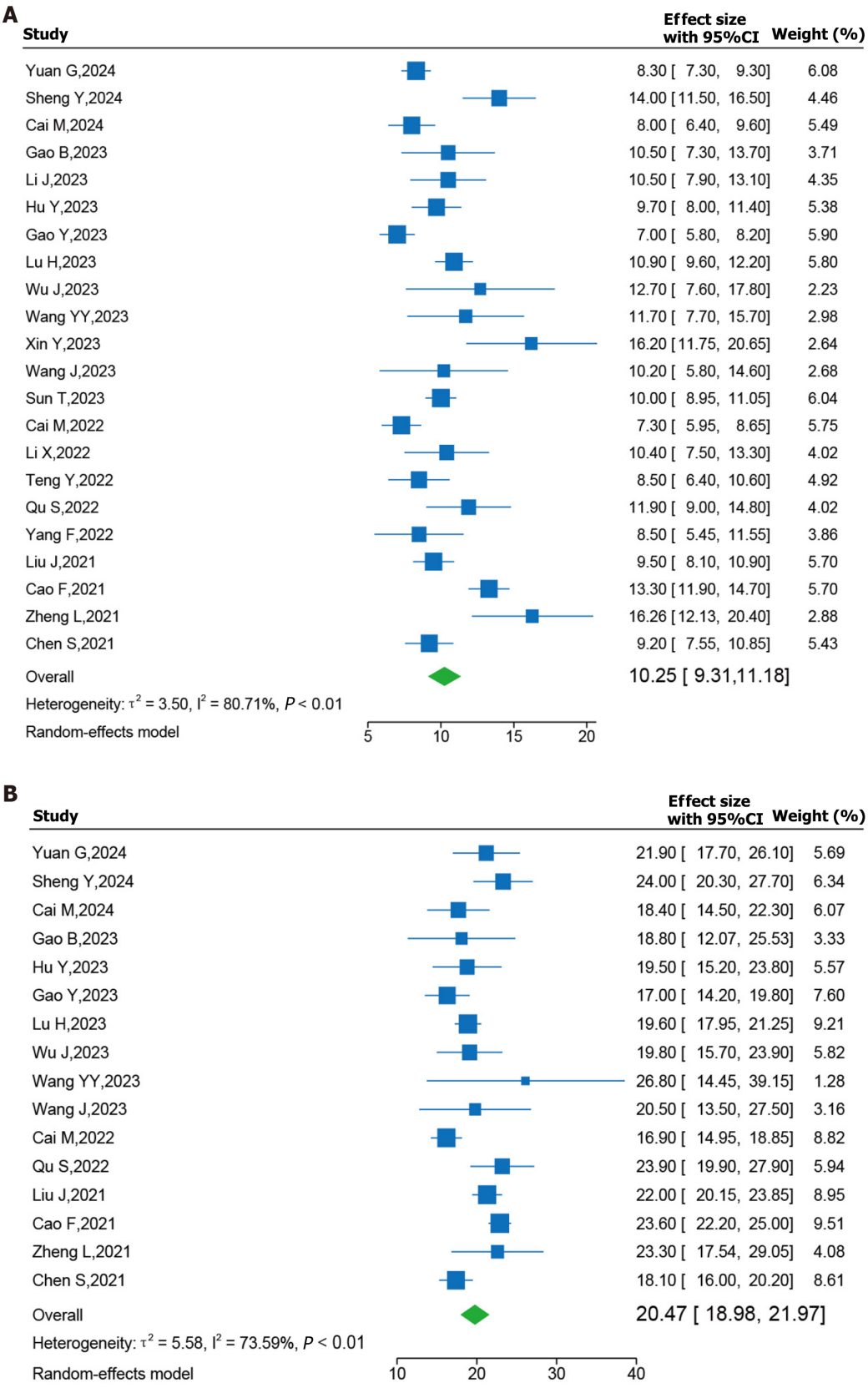
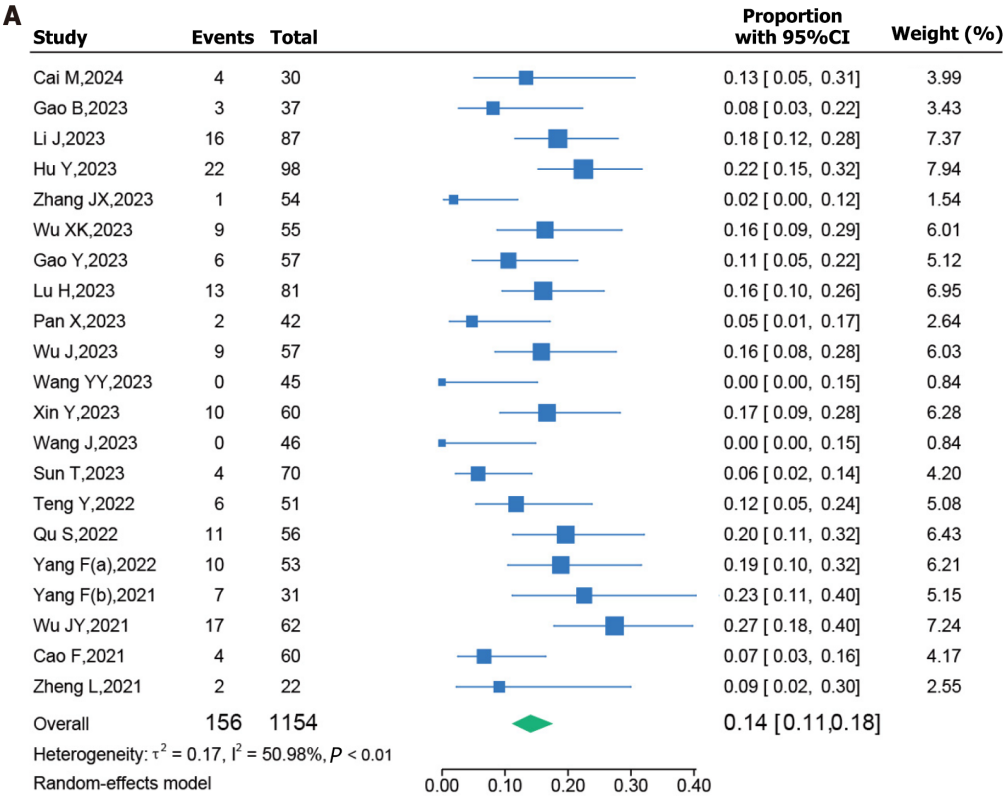


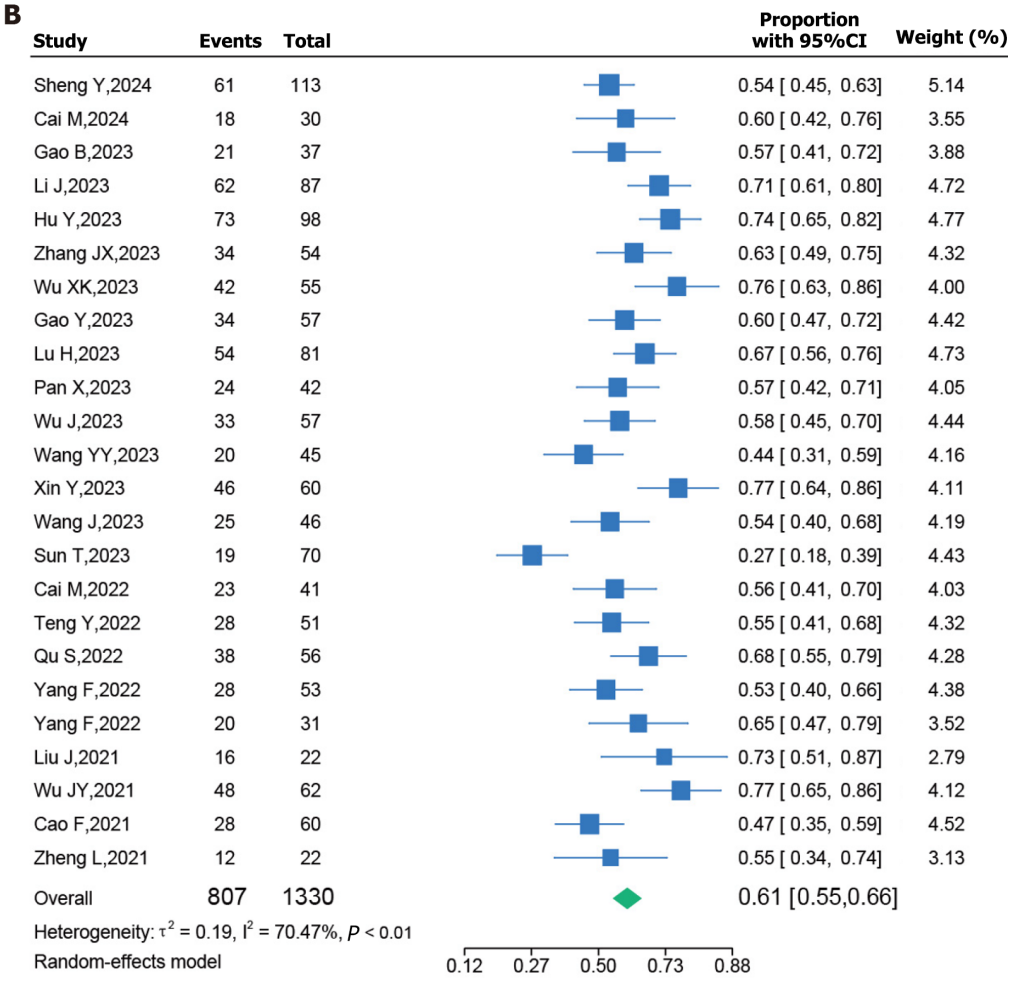
Figure 2 Forest plots of survival outcomes. A: The pooled effect size of median progression-free survival; B: The pooled effect size of median over survival.

studies and insufficient data on TACE, TKIs, and ICIs in some of the studies. Third, as all eligible studies were from China, our conclusions may not be widely relied upon and generalized because of the notable heterogeneity in etiology. Fourth, different treatment regimens of triple combination therapy could also be a major contributor to heterogeneity. Finally, the sequence of triple therapy administration was not uniform across the included studies, and a broad consensus on this is required in the future.

A


Study | Events | Total | Proportion with 95%CI | Weight (%)
Cai M,2024 4 30 0.13 [0.05, 0.31] 3.99
Gao B,2023 3 37 0.08 [0.03, 0.22] 3.43
Li J,2023 16 87 0.18 [0.12, 0.28] 7.37
Hu Y,2023 22 98 0.22 [0.15, 0.32] 7.94
Zhang JX,2023 1 54 0.02 [0.00, 0.12] 1.54
Wu XK,2023 9 55 0.16 [0.09, 0.29] 6.01
Gao Y,2023 6 57 0.11 [0.05, 0.22] 5.12
Lu H,2023 13 81 0.16 [0.10, 0.26] 6.95
Pan X,2023 2 42 0.05 [0.01, 0.17] 2.64
Wu J,2023 9 57 0.16 [0.08, 0.28] 6.03
Wang YY,2023 0 45 0.00 [0.00, 0.15] 0.84
Xin Y,2023 10 60 0.17 [0.09, 0.28] 6.28
Wang J,2023 0 46 0.00 [0.00, 0.15] 0.84
Sun T,2023 4 70 0.06 [0.02, 0.14] 4.20
Teng Y,2022 6 51 0.12 [0.05, 0.24] 5.08
Qu S,2022 11 56 0.20 [0.11, 0.32] 6.43
Yang F(a),2022 10 53 0.19 [0.10, 0.32] 6.21
Yang F(b),2021 7 31 0.23 [0.11, 0.40] 5.15
Wu JY,2021 17 62 0.27 [0.18, 0.40] 7.24
Cao F,2021 4 60 0.07 [0.03, 0.16] 4.17
Zheng L,2021 2 22 0.09 [0.02, 0.30] 2.55
Overall 156 1154 0.14 [0.11,0.18]
Heterogeneity: τ^2 = 0.17, I^2 = 50.98%, P < 0.01
Random-effects model
0.00 0.10 0.20 0.30 0.40

B


Study | Events | Total | Proportion with 95%CI | Weight (%)
Sheng Y,2024 61 113 0.54 [0.45, 0.63] 5.14
Cai M,2024 18 30 0.60 [0.42, 0.76] 3.55
Gao B,2023 21 37 0.57 [0.41, 0.72] 3.88
Li J,2023 62 87 0.71 [0.61, 0.80] 4.72
Hu Y,2023 73 98 0.74 [0.65, 0.82] 4.77
Zhang JX,2023 34 54 0.63 [0.49, 0.75] 4.32
Wu XK,2023 42 55 0.76 [0.63, 0.86] 4.00
Gao Y,2023 34 57 0.60 [0.47, 0.72] 4.42
Lu H,2023 54 81 0.67 [0.56, 0.76] 4.73
Pan X,2023 24 42 0.57 [0.42, 0.71] 4.05
Wu J,2023 33 57 0.58 [0.45, 0.70] 4.44
Wang YY,2023 20 45 0.44 [0.31, 0.59] 4.16
Xin Y,2023 46 60 0.77 [0.64, 0.86] 4.11
Wang J,2023 25 46 0.54 [0.40, 0.68] 4.19
Sun T,2023 19 70 0.27 [0.18, 0.39] 4.43
Cai M,2022 23 41 0.56 [0.41, 0.70] 4.03
Teng Y,2022 28 51 0.55 [0.41, 0.68] 4.32
Qu S,2022 38 56 0.68 [0.55, 0.79] 4.28
Yang F,2022 28 53 0.53 [0.40, 0.66] 4.38
Yang F,2022 20 31 0.65 [0.47, 0.79] 3.52
Liu J,2021 16 22 0.73 [0.51, 0.87] 2.79
Wu JY,2021 48 62 0.77 [0.65, 0.86] 4.12
Cao F,2021 28 60 0.47 [0.35, 0.59] 4.52
Zheng L,2021 12 22 0.55 [0.34, 0.74] 3.13
Overall 807 1330 0.61 [0.55,0.66]
Heterogeneity: τ^2 = 0.19, I^2 = 70.47%, P < 0.01
Random-effects model
0.12 0.27 0.50 0.73 0.88

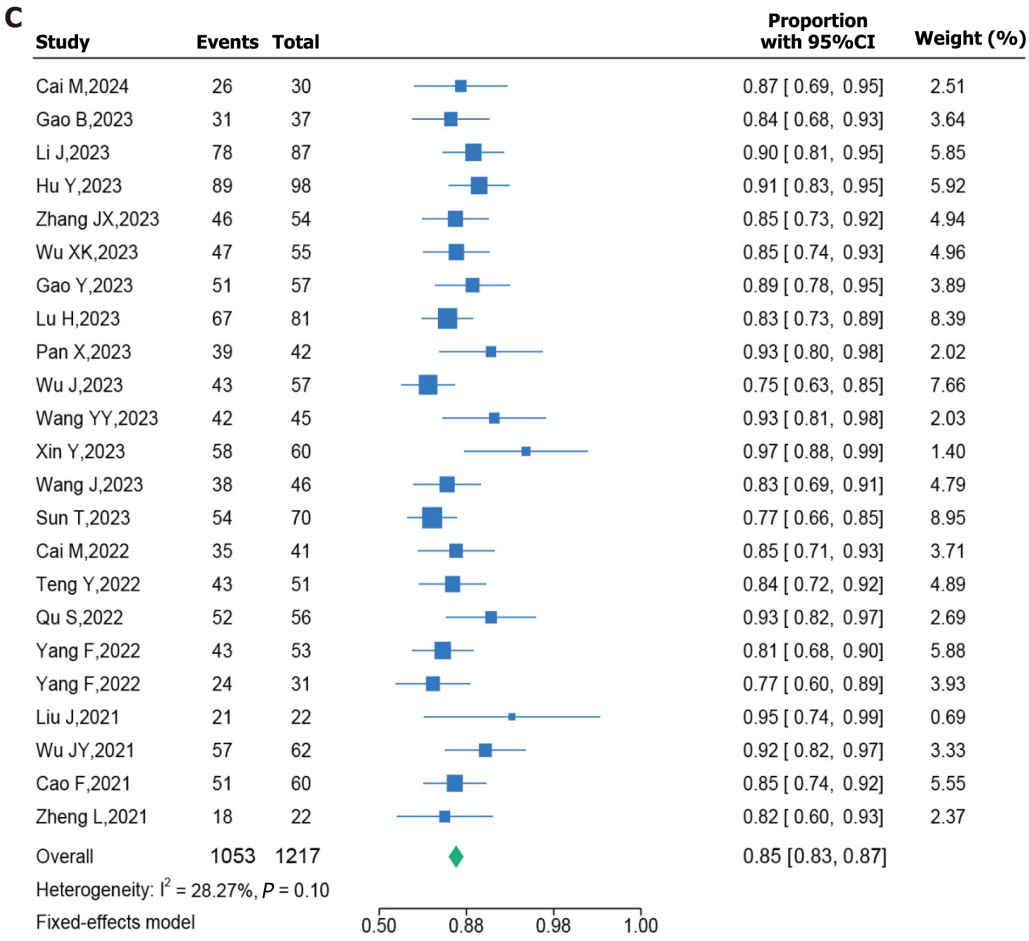


Figure 3 Forest plots of tumor responses. A: The pooled complete response rate; B: The pooled objective response rate; C: The pooled disease control rate.

CONCLUSION

We conducted a meta-analysis to evaluate the clinical efficacy and side effects of a combination of TACE with TKIs, and ICIs for unresectable HCC using current data. Our data support the potential application of triple therapy, which may have great clinical benefits for unresectable HCC in terms of tumor responses and survival outcomes without increasing the risk of severe AEs. Future randomized controlled trials with large sample sizes and multiple centers must be conducted to assess the efficacy and safety of the triple combination therapy and identify the optimal treatment regimen for potential beneficiaries with unresectable HCC.

Table 2 Ongoing clinical trials for triple therapy

Combination regimen	Comparator	Cancer stage	NCT number	Phase	Primary endpoint
TACE + lenvatinib + sintilimab/camrelizumab	None	Advanced unresectable HCC	NCT04997850	I/II	Conversion resection rate
TACE + lenvatinib + ICIs	None	Intermediate/advanced HCC	NCT04974281	I	Conversion resection rate
TACE + donafenib + ICIs	None	Advanced HCC	NCT05262959	II	PFS
TACE + sorafenib + ICIs	None	Intermediate/advanced HCC	NCT04518852	II	ORR, OS
TACE + sorafenib + tilelizumab	None	Advanced HCC	NCT04992143	II	1-yr survival rate
TACE + lenvatinib + tislelizumab	None	Advanced unresectable HCC	NCT05131698	I	ORR
TACE + sorafenib + tilelizumab	None	Advanced HCC	NCT04599777	II	OS
TACE + lenvatinib + durvalumab + tremelimumab	TACE	Locoregional HCC not amenable to curative therapy	NCT05301842	III	PFS

TACE + lenvatinib + pembrolizumab	TACE	Incurable/Non-metastatic HCC	NCT04246177	III	PFS, OS

PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; ICI: Immune checkpoint inhibitor.

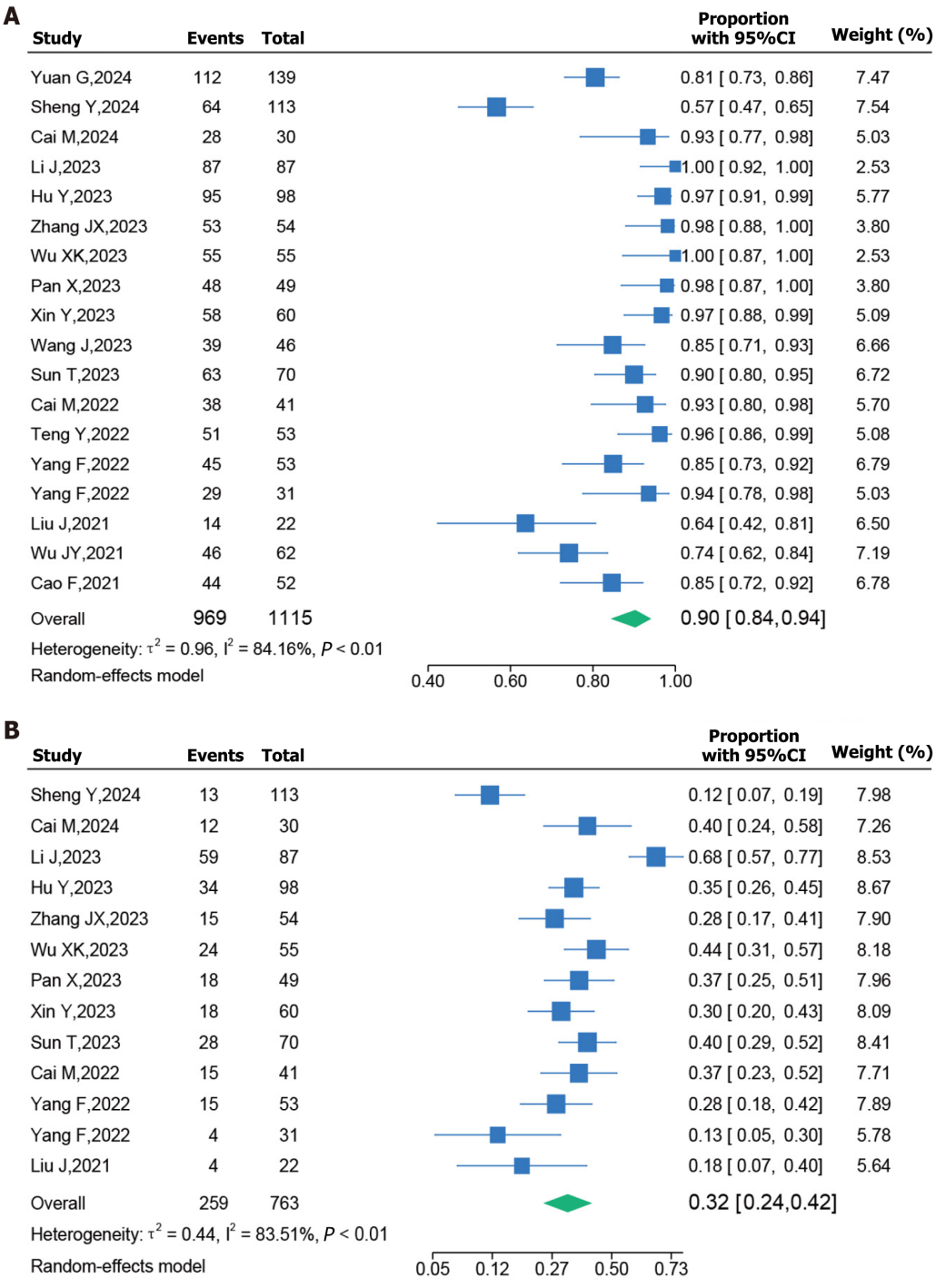


Figure 4 Forest plots of adverse events. A: The pooled rate of all-grade adverse events (AEs); B: The pooled rate of grade ≥ 3 AEs.

FOOTNOTES

Author contributions: Han F was responsible for acquisition of data, analysis and interpretation of data, drafting the article, final approval; Wang XH was responsible for interpretation of data, revising the article, final approval; Xu CZ was responsible for conception and design of the study, critical revision, final approval.

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