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Transarterial chemoembolization for hepatocellular carcinoma patients

Edited by
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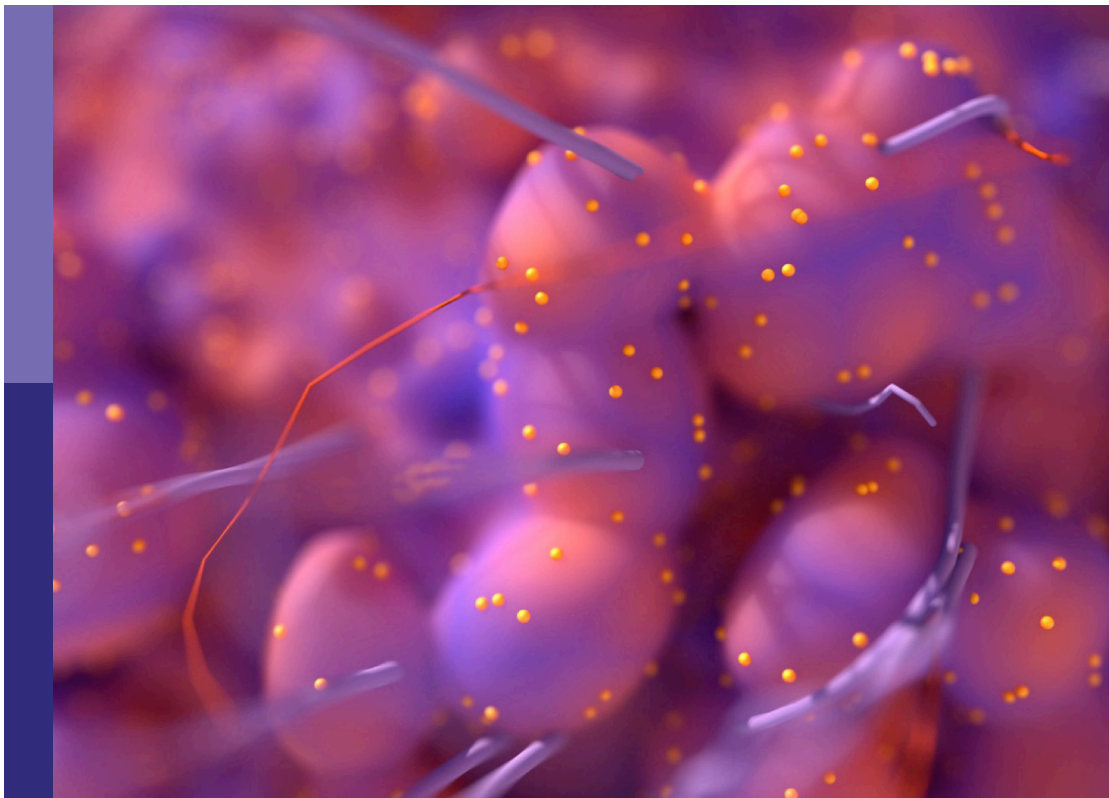

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Transarterial chemoembolization for hepatocellular carcinoma patients

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ORIGINAL RESEARCH
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Transarterial Chemoembolization Combined With Endoscopic Therapy Is Beneficial for Unresectable Hepatocellular Carcinoma With Esophagogastric Varices

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Background: The efficacy of transarterial chemoembolization (TACE) combined with endoscopic therapy for unresectable hepatocellular carcinoma with esophagogastric varices remains unclear.

Methods: The study has been registered on ClinicalTrials.gov with the number NCT05017922 (https://register.clinicaltrials.gov). Eligible patients were divided into combined group (received TACE plus endoscopic therapy) and control group (only received TACE). The occurrence of death and bleeding episodes during the follow-up was recorded. Kaplan–Meier analysis was used to compare outcomes between the two groups. Cox proportional hazard model was used to determine independent predictors for the survival.

Results: Eighty-nine patients were included, 42 in the combined group, others in the control group. During the follow-up, 51 patients died, the 1-year, 2-year, and 3-year survival rates were 64.9%, 45.5%, and 34.5%. The cumulative survival was significantly higher in the combined group than in the control group ($p = 0.027$); the 1-year, 2-year, and 3-year survival rates were 75.5%, 55.9%, 43.8% and 55.0%, 35.9%, 26.6%, respectively. Forty-four patients experienced bleeding, the bleeding rate was significantly higher in the control group than in the combined group (77.4% vs. 56.8%, $p = 0.016$). Multivariate analysis showed that treatment, hemoglobin, portal vein tumor thrombosis, and aspartate aminotransferase were independent predictors for overall survival; the first three factors were also independent predictors for bleeding-free survival. Patients who received primary prophylaxis had longer overall survival ($p = 0.042$) and bleeding-free survival ($p = 0.029$) than those who received secondary prophylaxis.

Conclusions: TACE combined with endoscopic therapy significantly improved survival and reduced bleeding rates in unresectable hepatocellular carcinoma with esophagogastric varices patients. Portal vein tumor thrombosis was a strong negative

prognostic factor for both overall survival and bleeding-free survival. Primary prophylaxis improved survival benefits compared with secondary prophylaxis.

Keywords: hepatocellular carcinoma, esophagogastric varices, transarterial chemoembolization, endoscopic variceal ligation, endoscopic injection sclerotherapy

1 INTRODUCTION

Liver cancer is the sixth most common malignancy and the third leading cancer-related mortality in the world (1). Due to the occult characteristics of the occurrence, about 70% of patients are diagnosed at an advanced stage and lose opportunities for surgical treatment (2). Transarterial chemoembolization (TACE) plays an important role as first-line therapy for unresectable hepatocellular carcinoma (HCC) and has been reported that it could improve 2-year survival when compared with conservative management for patients with unresectable HCC (OR = 0.53, 95% CI: 0.32–0.89, $p = 0.017$) (3). In addition, drug-eluting bead TACE is also considered as an effective down-staging treatment for unresectable HCC, with a down-staging success rate of 59.4%. In subsequent radical treatment, the complete response rate was 81.3% (4).

Liver cirrhosis results from a variety of causes can lead to HCC. An analysis showed that hepatitis B or hepatitis C is responsible for about 76% of the global incidence of the HCC (5). Portal hypertension is an important component in the natural history of liver cirrhosis, multiple portosystemic collaterals formatted when hepatic venous pressure gradient≥10 mmHg (6). Esophagogastric varices (EGV) is the most common form, which occurs in about 50% of liver cirrhosis patients. Since variceal hemorrhage is the major cause of death in patients with liver cirrhosis, with a 6-week mortality rate as high as 15%–20%, close monitoring and treatment are essential (7, 8). Endoscopic therapy, including endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS), is often used to provide primary and secondary prophylaxis of EGV and is considered to be the first-line treatment of acute esophagogastric variceal bleeding (EGVB) (9).

A propensity score matching study found that HCC patients with EGV had poorer liver functional reserve and that EGV was an independent risk factor for poor prognosis after TACE (10). Kim et al. (11) also demonstrated that in HCC patients, the occurrence of variceal bleeding could increase the risk of mortality (HR = 1.39, 95% CI: 1.06–1.82, $p = 0.015$), whereas primary prophylaxis of EGV could significantly reduce it (HR = 0.54, 95% CI: 0.33–0.88, $p = 0.014$). Emergency EVL has also been confirmed to be a safe and effective treatment for acute variceal hemorrhage in patients with HCC associated with portal vein tumor thrombosis (PVTT) (12). Since the efficacy of TACE combined with endoscopic therapy for unresectable HCC complicated with EGV remains unclear, we want to explore it and seek out predictors associated with survival through this non-randomized concurrent controlled trial to provide some reference for the treatment of such patients in the future.

Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; EGV, esophagogastric varices; EVL, endoscopic variceal ligation; EIS, endoscopic injection sclerotherapy; EGVB, esophagogastric varices bleeding; PVTT, portal vein tumor thrombosis; AST, aspartate aminotransferase; Hb, hemoglobin; OS, overall survival.

2 MATERIALS AND METHODS

2.1 Patients and Groups

All the eligible HCC patients treated in Qilu Hospital of Shandong University from 2017 to 2020 were evaluated prospectively and consecutively, who met the following inclusion criteria: (1) HCC was diagnosed in accordance with the 2017 edition of diagnosis guidelines (13), and all patients were in CNLC stage Ib to IIIa, and treated with TACE; (2) EGV was demonstrated through endoscopic examination; (3) Child-Pugh grade A or B, or grade C patients improved liver function to grade A or B through aggressive treatment; and (4) age between 18 and 75 years. The exclusion criteria were the following: (1) HCC with diffuse or distant metastasis, or with other systemic malignancies; (2) severe jaundice, hepatic encephalopathy, refractory ascites, or hepatorenal syndrome; (3) severe cardiac, cerebrovascular, lung, and renal diseases and cannot tolerate endoscopic treatment; (4) severe coagulation dysfunction; (5) severe infection, bleeding with unstable vital signs; (6) history of liver surgery; and (7) cannot or refuse to sign the informed consent.

Eligible patients were divided into two groups: combined group (received TACE plus endoscopic therapy) and control group (only received TACE); the treatment was decided by patients after they were informed of the risks and uncertain benefits of endoscopic therapy.

2.2 Study Design and Data Collection

Eligible patients were followed up and data were prospectively collected after receiving the standard treatment regimens to evaluate the efficacy of the therapy. Informed consents were obtained from all respondents, and the ethics of this study was approved by the Ethics Committee of Scientific Research of Qilu Hospital of Shandong University (No. 2016009). The study has been registered on ClinicalTrials.gov with the number NCT05017922.

The following data were collected: age, gender, etiology of the underlying liver disease, presence or absence of ascites, history of EGVB, alanine aminotransferase, aspartate aminotransferase (AST), total bilirubin, albumin, creatinine, hemoglobin (Hb), platelet, prothrombin time, alpha-fetoprotein, tumor number, tumor size, PVTT, Child-Pugh score, and BCLC stage.

2.3 Treatment

2.3.1 TACE

The 4-French catheter was inserted from the right femoral artery using the Seldinger technique, and the supplying artery of HCC was evaluated by visceral angiography. Then, the tip of the catheter was advanced into the left or right hepatic artery or tumor-feeding artery based on the tumor location and size. 5-Fu was injected first after safe fixed of the catheter. Then, the chemolipiodolization was performed, using oxaliplatin, epirubicin, and lipiodol. If stagnant flow did not show in the chemolipiodolization arterial territory, pure lipiodol was then injected. If the tumor-feeding artery still cannot be completely embolized, several absorbable gelatin sponge particles would be injected. The whole procedure was performed under fluoroscopy. This treatment regimen was conducted consistently in this study, regardless of tumor size and number.

2.3.2 Endoscopic Therapy

Symptomatic supportive treatment was given preoperatively to reduce portal venous pressure and correct anemia in all patients and ensure that vital signs were stable. After the site of esophageal varices was identified by the gastroscopy, spiral ligation using the EVL device (COOK, MBL-6-F) was performed and ensure the varices were fully inhaled, one to three rubber bands were used totally. After EVL, water was sprayed to the ligation sites to check for bleeding. If gastric varices were found, EIS was performed using the "sandwich method" of hypertonic glucose-tissue adhesive-normal saline. Make sure the needle entered the varicose vein before injecting drugs, and repeated the injection if necessary. When the EIS is accomplished, press on the puncture site to stop bleeding and then observe the sclerosis of varicose veins.

2.4 Follow-Up and Study Endpoints

After the first TACE, computerized tomography, and/or magnetic resonance imaging, tumor markers, liver function, and blood routine test were reexamined every 4–6 weeks. Subsequent TACE was determined according to the follow-up results. About two to four cycles of TACE were required for large HCC. Adjuvant radiofrequency ablation was given for all the small lesions found surrounding the primary lesions. Patients who received endoscopic therapy were reexamined 1–2 weeks after the first therapy, and subsequent endoscopic therapy was performed according to the varicose veins, until varicose veins disappeared or basically disappeared. After all the treatment was done, death and bleeding episodes were assessed every 3 months by phone call or outpatient service, then changed to every 6 months after a year of follow-up. It stopped in July 2020 or the day of death or the day of loss to follow-up or follow-up for 3 years.

2.5 Statistical Analysis

Data analysis was performed through the statistical software IBM SPSS Statistical 26.0 (SPSS Inc, Chicago, Illinois, USA). Continuous variables were expressed as the mean ± SD, whereas categorical variables were expressed as numbers. Continuous variables were compared using the Wilcoxon rank-sum test or Student's *t*-test, and categorical variables were compared using the Fisher exact test or Chi-square test. Kaplan–Meier analysis was used to compare cumulative survival and bleeding episodes between the two groups. Cox proportional hazard regression model was used to determine independent risk factors for the overall survival (OS) and bleeding-free survival. Statistical significance was considered when a two-tailed $p < 0.05$.

3 RESULTS

3.1 Patient Characteristics

A total of 89 patients diagnosed with unresectable HCC complicated with EGV were included in this study during 2017–2020. The median age was 59 years (range from 32 to 78 years), 76 were males and 13 were females. The characteristics of the included patients are listed in **Table 1**. In the combined group ($n = 42$), 88.1% were males, and the mean age and Child-Pugh score were 58.4 ± 7.6 years and 6.9 ± 1.6, respectively. The etiologies of underlying liver disease were hepatitis B ($n = 35$, 83.3%), hepatitis C ($n = 2$, 4.8%), and alcoholic hepatitis ($n = 5$, 11.9%). Twenty-four (57.1%) developed ascites, 24 (57.1%) had a history of EGVB, and 10 (23.8%) had PVTT. Twenty-one of them were Child-Pugh grade A, 18 were grade B, and 3 improved from grade C to grade B. In the control group ($n = 47$), 83.0% were males, and the mean age and Child-Pugh score were 58.0 ± 9.7 years and 6.3 ± 1.5, respectively. The etiologies of underlying liver disease were hepatitis B ($n = 43$, 91.5%), hepatitis C ($n = 1$, 2.1%), and alcoholic hepatitis ($n = 3$, 6.4%). Eighteen (38.3%) developed ascites, 23 (48.9%) had a history of EGVB, and 15 (31.9%) had PVTT. Twenty-nine of them were Child-Pugh grade A, 16 were grade B, and 2 improved from grade C to grade B. None of the included patients have received systemic chemotherapy or immunotherapy during the follow-up period. No significant difference in these characteristics was found.

3.2 Overall Survival

There were 51 patients who died during the follow-up, 21 in the combined group and 30 in the control group; 9 (42.9%) patients died from bleeding in the combined group, and 17 (56.7%) in the control group. The survival period of the whole group was 1–36 months (median, 21 months); the 1-year, 2-year, and 3-year survival rates were 64.9%, 45.5%, and 34.5% (**Figure 1A**). The cumulative survival was significantly higher in the combined group than in the control group ($p = 0.027$), with the median survival being 32 and 16 months, and the 1-year, 2-year, and 3-year survival rates were 75.5%, 55.9%, 43.8% and 55.0%, 35.9%, 26.6%, respectively (**Figure 1B**).

3.3 Bleeding Episodes

There were 44 patients who experienced bleeding during the follow-up, 18 in the combined group and 26 in the control group. The bleeding rate was significantly higher in the control group than in the combined group (77.4% vs. 56.8%, $p = 0.016$) (**Figure 2**).

TABLE 1 | Baseline characteristics of all patients in the two groups.

Characteristics	Combined group (*n* = 42)	Compared group (*n* = 47)	*p*-value
Age (years)	58.4 ± 7.6	58.0 ± 9.7	0.838
Sex (male/female)	37/5	39/8	0.495
Etiology (*n*)			
Hepatitis B	35	43	0.517
Hepatitis C	2	1	
Alcoholic Hepatitis	5	3	
Ascites (*n*)	24	18	0.164
EGVB (*n*)	24	23	0.439
ALT (U/L)	41.4 ± 36.3	49.0 ± 34.9	0.318
AST (U/L)	51.9 ± 33.3	63.1 ± 43.2	0.180
TBIL (μmol/L)	24.8 ± 12.2	32.1 ± 43.3	0.295
Alb (g/L)	37.0 ± 5.3	36.7 ± 6.7	0.783
Cr (mg/dl)	69.3 ± 14.8	65.9 ± 14.0	0.263
Hb (g/L)	111.4 ± 30.9	116.3 ± 28.6	0.443
PLT ($\times 10^9$/L)	96.1 ± 69.2	100.3 ± 53.5	0.751
PT (s)	14.4 ± 2.1	13.7 ± 2.0	0.110
AFP (ng/ml)	1,703.0 ± 5,357.2	3,055.5 ± 7,141.0	0.335
Tumor number (*n*)			
1	18	25	0.330
≥2	24	22	
Tumor size (*n*)			
<5 cm	36	33	0.080
≥5 cm	6	14	
PVTT (*n*)	10	15	0.396
Child-Pugh score	6.9 ± 1.6	6.3 ± 1.5	0.121
Child-Pugh grade (*n*)			
A	21	29	0.567
B	18	16	
C	3	2	
BCLC stage (*n*)			
A2	7	10	0.337
A3	9	15	
A4	0	1	
B	26	21	

Values are expressed as mean ± SD. Abbreviations: EGVB, esophagogastric varices bleeding; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; Alb, albumin; Cr, creatinine; Hb, hemoglobin; PLT, platelet; PT, prothrombin time; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer.

3.4 Predictors of OS

All the baseline data of the patients were analyzed through univariate and multivariate Cox proportional hazard regression model to explore possible predictors of OS. The univariate analysis showed that treatment (HR = 0.539, 95% CI: 0.307–0.946, $p = 0.031$), Child-Pugh score (HR = 1.227, 95% CI: 1.035–1.454, $p = 0.019$), Hb (HR = 0.990, 95% CI: 0.981–0.999, $p = 0.030$), AST (HR = 1.010, 95% CI: 1.004–1.015, $p = 0.001$), alanine aminotransferase (HR = 1.009, 95% CI: 1.002–1.017, $p = 0.011$), albumin (HR = 0.945, 95% CI: 0.903–0.989, $p = 0.015$), total bilirubin (HR = 1.011, 95% CI: 1.004–1.017, $p = 0.001$), and PVTT (HR = 3.913, 95% CI: 2.163–7.078, $p < 0.01$) were risk factors for OS. The multivariate analysis showed that treatment (HR = 0.520, 95% CI: 0.277–0.977, $p = 0.042$), Hb (HR = 0.985, 95% CI: 0.974–0.996, $p = 0.006$), AST (HR = 1.010, 95% CI: 1.001–1.020, $p = 0.033$), and PVTT (HR = 4.441, 95% CI: 2.336–8.440, $p < 0.01$) were independent prognostic factors for OS (**Table 2**).

3.5 Predictors of Bleeding-Free Survival

All the baseline data of the patients were analyzed through univariate and multivariate Cox proportional hazard regression model to explore possible predictors of OS. The univariate analysis showed that treatment (HR = 0.487, 95% CI: 0.265–0.894, $p = 0.020$), Child-Pugh score (HR = 1.224, 95% CI: 1.020–1.470, $p = 0.030$), Hb (HR = 0.983, 95% CI: 0.974–0.993, $p = 0.001$), AST (HR = 1.007, 95% CI: 1.001–1.014, $p = 0.024$), total bilirubin (HR = 1.010, 95% CI: 1.001–1.018, $p = 0.022$), PVTT (HR = 4.071, 95% CI: 2.045–8.104, $p < 0.01$), and history of EGVB (HR = 2.315, 95% CI: 1.223–4.382, $p = 0.010$) were risk factors for bleeding-free survival. The multivariate analysis showed that treatment (HR = 0.384, 95% CI: 0.190–0.773, $p = 0.007$), Hb (HR = 0.973, 95% CI: 0.955–0.991, $p = 0.003$), and PVTT (HR = 4.829, 95% CI: 2.231–10.452, $p < 0.01$) were independent prognostic factors for bleeding-free survival (**Table 3**).

3.6 Effects of PVTT on OS and Bleeding Episodes

According to the correlation analysis, we found that the occurrence of PVTT was significantly negatively correlated with OS and bleeding-free survival. Based on this finding, we respectively compared OS and bleeding episodes with or without PVTT.

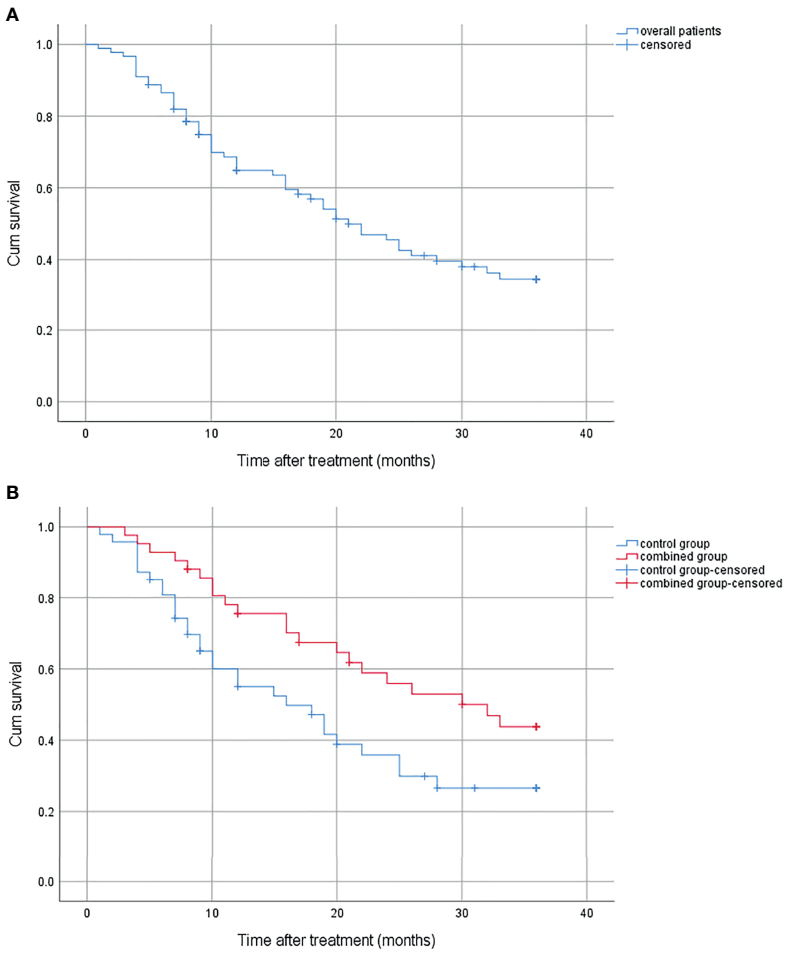

FIGURE 1 | **(A)** Cumulative survival for overall patients. **(B)** Cumulative survival for the combined group and the control group.

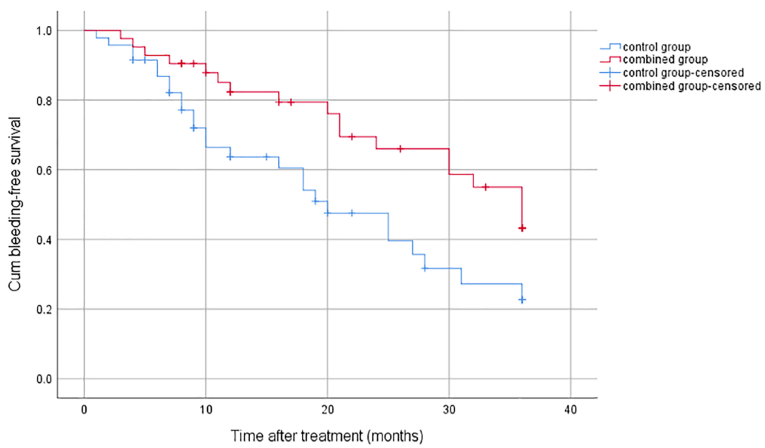

FIGURE 2 | Cumulative bleeding-free survival for the combined group and the control group.

TABLE 2 | Univariate and multivariate analysis of predictors for OS.

Variables	Univariate analysis		Multivariate analysis		
	HR	*p*-value	HR	95% CI	*p*-value
Age (years)	1.012	0.489			
Sex (male/female)	1.194	0.663			
Etiology	1.551	0.352			
Ascites	1.110	0.710			
EGVB	1.552	0.126			
ALT (U/L)	1.009	0.011	0.995	0.984–1.006	0.364
AST (U/L)	1.010	0.001	1.010	1.001–1.020	0.033
TBIL (μmol/L)	1.011	0.001	1.004	0.995–1.012	0.390
Alb (g/L)	0.945	0.015	0.989	0.924–1.058	0.739
Cr (mg/dl)	0.998	0.824			
Hb (g/L)	0.990	0.030	0.985	0.974–0.996	0.006
PLT ($\times10^9$/L)	1.002	0.347			
PT (s)	1.113	0.136			
AFP (ng/ml)	1.000	0.005			
Tumor number	1.085	0.772			
Tumor size (cm)	1.301	0.441			
PVTT	3.913	<0.01	4.441	2.336–8.440	<0.01
Child-Pugh score	1.227	0.019	1.075	0.806–1.435	0.622
BCLC stage	1.173	0.573			
Treatment	0.539	0.031	0.520	0.277–0.977	0.042

OS, overall survival; HR, hazard ratio; CI, confidence interval; EGVB, esophagogastric varices bleeding; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; Alb, albumin; Cr, creatinine; Hb, hemoglobin; PLT, platelet; PT, prothrombin time; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer.

No matter what kind of treatment was conducted, patients with PVTT had worse OS than those without. In the combined group, the 1-year, 2-year, and 3-year survival rate were 42.0%, 0%, 0% and 84.4%, 67.3%, 52.7% for patients with and without PVTT ($p < 0.01$), respectively (**Figure 3A**). In the control group, the 1-year, 2-year, and 3-year survival rate were 26.7%, 17.8%, 0% and 68.7%, 45.0%, 35.4% for patients with and without PVTT ($p = 0.003$), respectively (**Figure 3B**).

Patients with PVTT also had worse bleeding-free survival than those without, regardless of treatment method. In the combined group, the bleeding rate was 72% and 49.5% for patients with and without PVTT ($p < 0.01$), respectively

TABLE 3 | Univariate and multivariate analysis of predictors for bleeding-free survival.

Variables	Univariate analysis		Multivariate analysis		
	HR	*p*-value	HR	95% CI	*p*-value
Age (years)	1.027	0.167			
Sex (male/female)	1.174	0.716			
Etiology	1.712	0.306			
Ascites	1.160	0.623			
EGVB	2.315	0.010	0.796	0.275–2.308	0.674
ALT (U/L)	1.007	0.128			
AST (U/L)	1.007	0.024	1.004	0.996–1.011	0.310
TBIL (μmol/L)	1.010	0.022	1.005	0.996–1.014	0.299
Alb (g/L)	0.952	0.058			
Cr (mg/dl)	1.000	0.992			
Hb (g/L)	0.983	0.001	0.973	0.955–0.991	0.003
PLT ($\times10^9$/L)	1.002	0.544			
PT (s)	1.091	0.277			
AFP (ng/ml)	1.000	0.008			
Tumor number	0.962	0.897			
Tumor size (cm)	1.403	0.347			
PVTT	4.071	<0.01	4.829	2.231–10.452	<0.01
Child-Pugh score	1.224	0.030	1.034	0.822–1.301	0.777
BCLC stage	1.075	0.811			
Treatment	0.487	0.020	0.384	0.190–0.773	0.007

HR, hazard ratio; CI, confidence interval; EGVB, esophagogastric varices bleeding; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; Alb, albumin; Cr, creatinine; Hb, hemoglobin; PLT, platelet; PT, prothrombin time; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombosis; BCLC, Barcelona Clinic Liver Cancer.

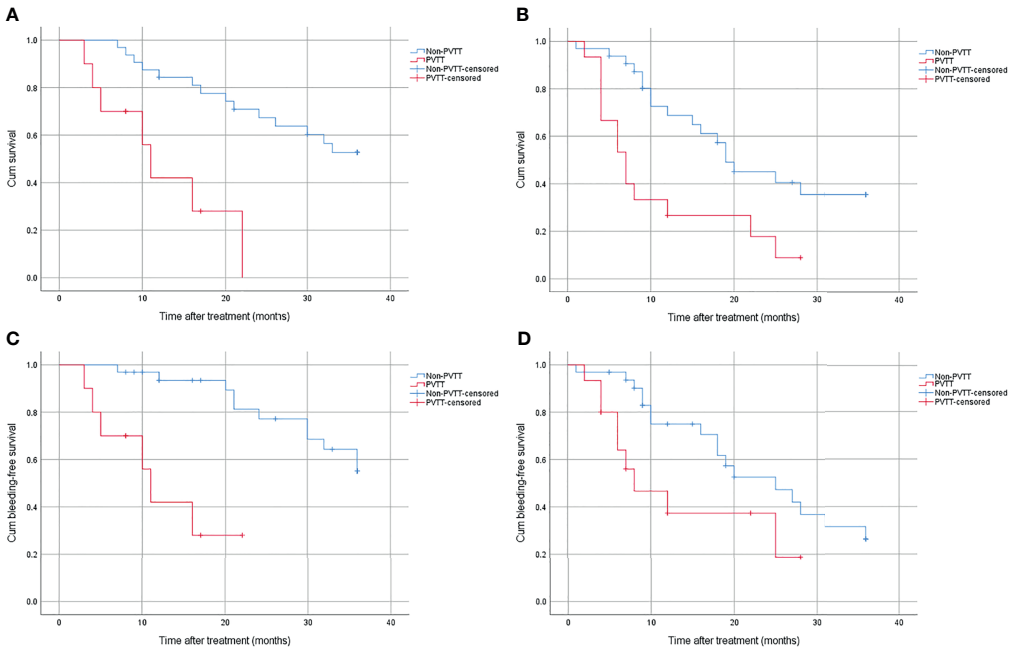

FIGURE 3 | **(A)** Cumulative survival for patients with or without PVTT in the combined group. **(B)** Cumulative survival for patients with or without PVTT in the control group. **(C)** Cumulative bleeding-free survival for patients with or without PVTT in the combined group. **(D)** Cumulative bleeding-free survival for patients with or without PVTT in the control group.

(**Figure 3C**). In the control group, the bleeding rate was 81.3% and 73.7% for patients with and without PVTT (p = 0.033), respectively (**Figure 3D**).

3.7 Effects of Primary Prophylaxis on OS and Bleeding Episodes

There were 16 patients who received primary prophylaxis in the combined group. The cumulative survival was significantly higher in patients who received primary prophylaxis than those who received secondary prophylaxis, with 1-year, 2-year, and 3-year survival rates of 80.8%, 80.8%, 71.8% and 72.4%, 43.6%, 29.4% (p = 0.042), respectively (**Figure 4A**). The bleeding rate was significantly higher in the latter (19.2% vs. 65.3%, p = 0.029) (**Figure 4B**).

4 DISCUSSION

This is the first prospective study to demonstrate that TACE combined with endoscopic therapy significantly improved survival and reduced bleeding rates in patients with unresectable HCC complicated with EGV. We observed that TACE combined with endoscopic therapy yielded survival outcomes significantly superior to TACE alone for unresectable HCC complicated with EGV, with 1-year, 2-year, and 3-year survival rates of 75.5%, 55.9%, 43.8% and 55.0%, 35.9%, 26.6% (p = 0.027), and the bleeding rate was 56.8% and 77.4% (p = 0.016), respectively. Treatment, Hb, PVTT, and AST were independent prognostic factors for OS; the first three factors were also independent prognostic factors for bleeding-free survival. No matter what kind of treatment was conducted, patients with PVTT had worse OS and bleeding-free survival than those without. Patients who received primary prophylaxis had longer overall survival (p = 0.042) and bleeding-free survival (p = 0.029) than those who received secondary prophylaxis.

Studies have shown that the in-hospital mortality rate of HCC patients with variceal hemorrhage was as high as 20.5%, and their OS was worse than those without EGVB (median, 3.5 vs. 7.5 months, p < 0.001), indicating that the occurrence of EGV significantly affects the survival of HCC, and it has a great possibility to induce death by causing bleeding before the HCC progresses (14). Therefore, the prevention of variceal bleeding is very necessary to improve the survival of HCC. Endoscopic therapy has been widely used in the primary and secondary prophylaxis of EGV. Our results showed that endoscopic therapy combined with TACE could significantly improve outcomes for unresectable HCC patients complicated with EGV, especially in patients who received primary prophylaxis, which is consistent with previous studies (15). Chen et al. (16) performed secondary prophylactic endoscopic therapy for EGVB on 192 HCC patients and found that it could provide survival benefits for these patients whether through EVL or EIS, with 6-month, 1-year, and 5-year cumulative rebleeding rates of 40.9%, 49.3%, and 71.2%, and cumulative mortality rates of 33.5%, 45.8%, and 65.7%, respectively. Kim et al. (11) affirmed the effectiveness of primary prophylaxis in HCC patients, with 1- and 3-year

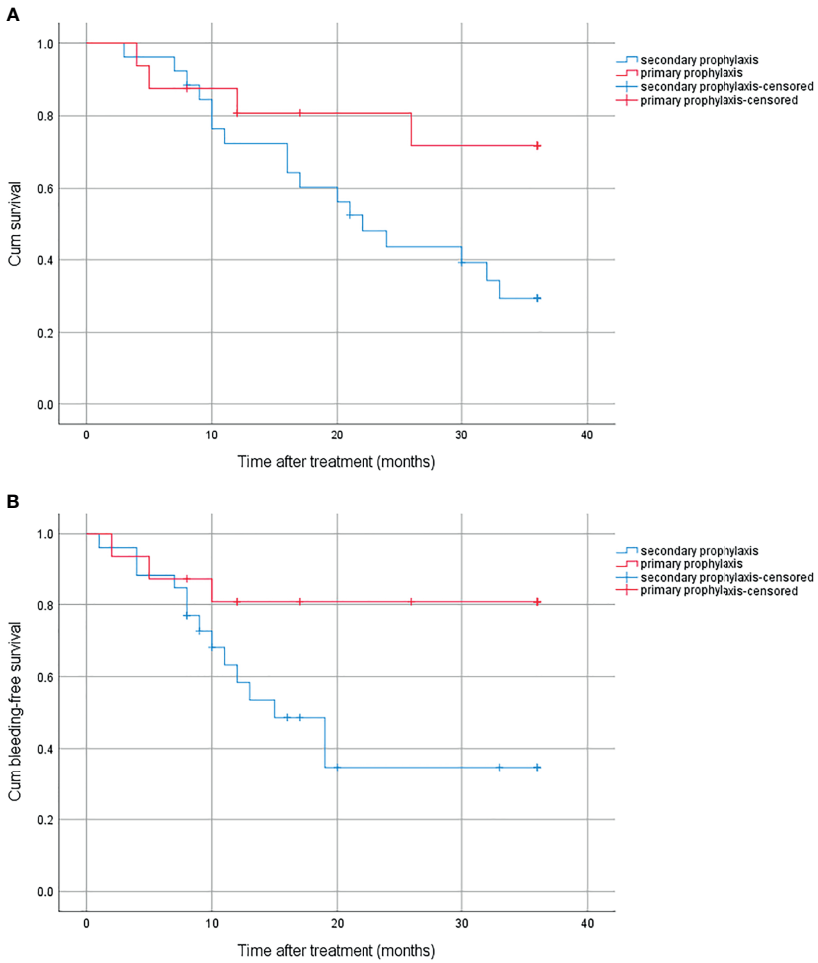

FIGURE 4 | **(A)** Cumulative survival for primary prophylaxis and secondary prophylaxis. **(B)** Cumulative bleeding-free survival for primary prophylaxis and secondary prophylaxis.

cumulative variceal bleeding rates of 20.4% and 30.4%, respectively. This suggested that primary prophylaxis was superior to secondary prophylaxis in reducing the risk of rebleeding.

We also found that, in addition to treatment method, levels of Hb and AST, and PVTT status could influence outcomes of patients. These have also been demonstrated in previous studies. Low levels of Hb were considered to be an independent risk factor of rebleeding after EVL treatment in liver cirrhosis patients with esophageal varices (OR = 17.3491, 95% CI: 4.00–75.34, $p = 0.005$) (17). The occurrence of early ascites after drug-eluting bead TACE in HCC patients was associated with poor prognosis (median OS, 17 months), which was revealed to be influenced by levels of Hb before treatment (18). In patients with spontaneous ruptured HCC who were treated with TACE, higher Hb was independently associated with 30-day survival (OR = 0.609, $p = 0.036$) (19). Higher Hb after TACE combined with external beam radiotherapy for unresectable HCC was a predictor of successful treatment ($p = 0.016$) (20).

As an indicator of liver function, AST represents the degree of liver damage and the reserve of liver function. Liver injury from any causes can lead to elevated AST in the blood. In HCC patients who have undergone radical hepatectomy, AST could be used to predict early postoperative recurrence and post-recurrence survival (21). Low levels of alanine aminotransferase-to-AST ratio was associated with longer survival in primary HCC patients ($p < 0.05$) (22).

PVTT is the most common form of macrovascular invasion of HCC, which is found in approximately 10%–60% patients at the time of diagnosis of HCC (23, 24). It is a strong negative prognostic factor, and once it is present, HCC is classified into advanced stage, with an OS ranging from 2 to 4 months if only treated with conservative treatment (25). Portal vein pressure increased due to the PVTT and then numerous collateral veins around the obstructed portal vein formed, which may lead to the development or aggravation of EGV and increase the potential bleeding complications (26). Lim et al. (27) demonstrated that patients with PVTT had a higher proportion of high-risk varices (23.0 vs. 13.3%, $p = 0.003$) and cumulative variceal bleeding rate (4.5

vs. 0.4% at 1 year, $p = 0.009$) than those without, and Vp4 PVTT was an independent predictor for high-risk varices (aOR = 3.345, 95% CI: 1.457–7.680, $p < 0.05$). TACE may provide survival benefits for HCC patients with PVTT, and can be safely performed as long as liver function is good and collateral circulation around the embolization site is abundant (28). Niu et al. (29) found that TACE could significantly improve survival compared with conservative treatment for HCC with any type of PVTT (OS, 8.67 vs. 1.4 months, $p < 0.001$), and the extent of PVTT was independent prognostic factors (OR = 1.856, 95% CI: 1.449-2.377, $p < 0.001$). Similar conclusions were also confirmed by Luo et al. (30).

There are some limitations in our study. First, the non-randomized design of this study introduces a potential selected bias that needs randomized trial to reduce it. Second, the single-center study with a small sample size and relatively short study period, and HBV infection as the main etiology, entails that the extrapolation of the conclusion needs to be further verified. Third, adjuvant radiofrequency ablation was given for all the small lesions found surrounding the primary lesions; whether it has an influence on the survival benefit still needs further verification.

5 CONCLUSION

We observed that TACE combined with endoscopic therapy significantly improved survival and reduced bleeding rates in patients with unresectable HCC complicated with EGV. PVTT was a strong negative prognostic factor for both OS and bleeding-free survival. Primary prophylaxis improved survival benefits compared with secondary prophylaxis. Multicenter prospective randomized control trials are still needed to verify the accuracy of the conclusions in the future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Qilu Hospital of Shandong University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZT, YR, and ZP contributed to conception and design of the study. YR and ZP collected the data. ZT and YR performed the statistical analysis. ZT wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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Transarterial Chemoembolization Combined With Tyrosine Kinase Inhibitors for Intermediate-Stage Hepatocellular Carcinoma, What Else Can We Do?

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Transarterial chemoembolization (TACE) has been considered the standard treatment for intermediate-stage hepatocellular carcinoma (HCC). However, intermediate-stage HCC is highly heterogeneous with a broad population with varying tumour burdens, liver function. This suggests that TACE monotherapy treatment might not be suitable for all patients with intermediate-stage HCC. The administration of tyrosine kinase inhibitors (TKIs) has become an important treatment option for improving the prognosis of patients with advanced HCC. Over the years, several trials have been conducted to explore the effects of TACE combined with TKIs for intermediate-stage HCC. However, the clinical efficacy is still controversial, and its potential clinical utility needs to be confirmed. This review will focus on the recent progress of TACE combined TKIs for intermediate-stage HCC.

Keywords: hepatocellular carcinoma, intermediate stage, tyrosine kinase inhibitors, transarterial chemoembolization, combination therapy

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths worldwide, and the prognosis of unresectable HCC is poor (1, 2). Chronic liver disease caused by hepatitis B and C viral infections is an important pathogenic factor for HCC (3, 4). However, with the anti-viral treatment in recent years, most HCC patients developed from hepatitis virus infection have decreased. In addition, non-alcoholic fatty liver disease (NAFLD) has gradually become prominent with increasing numbers of patients with diabetes mellitus, obesity, and hyperlipidemia (5–8). Approximately 20-30% of patients with NAFLD develop non-alcoholic steatohepatitis (NASH), and 10-20% of that develop cirrhosis (9, 10). Additional HCC patients are expected worldwide with the advances in surveillance programs and early diagnosis. The patients with intermediate-stage HCC do not often benefit from the transarterial chemoembolization (TACE) procedure due to its heterogeneity (11, 12). More and more physicians realize the importance of intermediate-stage HCC substaging. According to the 2022 Barcelona Clinic Liver Cancer (BCLC) version stratifies, TACE is only suitable for patients with well-defined nodules, preserved portal flow, and selective access (13). In addition, incomplete TACE embolization can

induce the overproduction of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which may promote tumor recurrence or metastasis (14, 15). Since most HCC patients have typically developed advanced stages with inferior prognosis, it is essential to prolong the patient's duration in the intermediate-stage HCC. The Food and Drug Administration (FDA) approves tyrosine kinase inhibitors (TKIs) for the treatment of advanced HCC because they can suppress tumor angiogenesis *via* the inhibition of multiple receptor (16). Recently, the combination of TACE with TKIs, such as sorafenib, has been confirmed to be a feasible and safe treatment (17–19). This review will attempt to analyze the present status of TACE combined TKIs for intermediate-stage HCC.

TACE

The operative approach of conventional-TACE (cTACE) is to infuse a chemotherapy agent and lipiodol emulsions into the tumor-feeding arteries through a catheter under the guidance of medical imaging technology, followed by an injection of gelatin sponge particles to embolize the blood vessels (20). There are studies indicating that cTACE may significantly prolong survival in cases of intermediate-stage HCC compared with supportive care (21, 22). Some studies have shown that patients who respond to cTACE have a better prognosis and long-term survival (23, 24).

Although cTACE has been proven to have survival benefits for patients with intermediate-stage HCC, no optimal technique has been established (25). Due to the operator's instability, the patient's prognosis may also differ to a certain extent (26, 27). Drug-eluting beads transarterial chemoembolization (DEB-TACE) is to load chemotherapy drugs onto drug-loaded microsphere and then deliver them to the feeding artery of the hepatic tumor (28). This technology can achieve the sustained release of the chemotherapy drugs in the local tumor and reduce systemic exposure (29–31). Compared with the intra-arterial injection of chemotherapeutic drugs with or without lipiodol, DEB-TACE significantly reduces plasma concentrations of chemotherapeutic agents (32). Meanwhile, a previous study investigated serum VEGF level response after TACE with different embolic agents in patients with HCC and reported cTACE group had a more extraordinary rise in the circulating plasma levels of VEGF compared to the DEB-TACE group for 24-hour post-TACE and during the 4-week follow-up (114% vs. 164%, p=0.01; 123% vs. 170%, p=0.03) (33). This result indicates that DEB-TACE may better control tumors' local recurrence and metastasis. However, many studies have compared the effectiveness of cTACE and DEB-TACE, and the results show that there is no statistical difference in the median overall survival (mOS) (34–37). For adverse events, DEB-TACE does not seem to perform better than cTACE. In the PRESCISION V study, there is no statistical difference (p=0.86) between cTACE (19.4%) and DEB-TACE (20.4%) in serious adverse events within 30 days after TACE (34). Recently, Zhang et al. showed that DEB-TACE caused more hepatobiliary injuries and severe abdominal pain (38).

Different sizes of DEBs may also influence the therapeutic effect of HCC patients. There are currently numerous bead sizes for clinical use. Some studies demonstrated that smaller DEBs enable more distal embolization, greater penetration, and tumor necrosis (39–41). Previously, multiple studies have demonstrated the effectiveness and safety of small-size DEBs for HCC patients, indicating that small-size DEBs have better application prospects for HCC patients (42–47).

The current clinical evidence was not sufficient to prove the superiority of DEB-TACE over cTACE. Thus, more high-quality clinical studies are certainly needed. The development of DEBs and the update of embolization technology also provide new options for the local treatment of intermediate-stage HCC.

TKIs

Most HCC nodules are supplied by the hepatic artery. Angiogenesis plays a vital role in tumor occurrence, development, invasion, and metastasis (48). Angiogenesis of HCC is predominantly related to the out-of-control information transmission of cells in the tumor. The main pathway included epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), HGF/C-Met and fibroblast growth factor receptor (FGFR). These receptors' activation further triggers the cascade of intracellular RAS/RAF/MEK/ERK protein kinase signaling, leading to an imbalance between pro and anti-angiogenesis (4, 49). In an animal study, researchers prepared the iodine 124-labeled iodoazomycin galactopyranoside as a PET tracer for imaging and found that the oxygen content in the tumor was significantly lower than that of normal liver cells in the mouse (50). This finding may indicate that liver tumor cells are in a hypoxic microenvironment, and hypoxia can strongly stimulate tumor angiogenesis (51–53). The generated abnormal tumor blood vessels can interfere with the treatment of HCC. Therefore, we can improve the treatment efficacy of HCC through improving hypoxic microenvironment of tumor cells and normalizing the tumor vasculature. VEGF is widely considered an essential regulator of HCC tumor-induced angiogenesis. Overexpression of VEGF can cause uneven blood flow distribution and oxygen delivery in tumor blood vessels (54, 55). TKIs drugs can act on different kinase receptors. For example, sorafenib, which was first approved for the treatment of advanced HCC, can act on receptors such as VEGFR1-3, PDGFR-β, C-kit, RET, and PLT3, and extending the survival of patients with advanced HCC by blocking the information transmission of tumor cells, inhibiting tumor angiogenesis, promoting the normalization of tumor blood vessels (56, 57).

INTERMEDIATE-STAGE HCC (BCLC STAGE B)

Intermediate-stage HCC is highly heterogeneous with a broad population. The differences were mainly reflected in the clinical characteristics, liver function, performance status, and tumor

burden. For long times, TACE has been the standard and effective therapy for intermediate-stage HCC. However, this treatment is not suitable for all patients with intermediate-stage HCC (12). TACE is suitable for some patients with a small tumor burden and well-preserved liver function (58, 59). Previous randomized studies have shown that in selected patients with good liver function, the three-year survival rate of the TACE group is only 30% (60). Many patients require repeated TACE treatment because of incomplete embolization, which may deteriorate hepatic function and poor outcomes (61, 62).

The screening and stratification of the suitable population for TACE is essential. Some studies have performed the subclassification of the intermediate-stage group and the design of treatment strategies. In 2012, a panel of experts first divided stage B HCC patients into stages B1-B4 and proposed the "beyond Milan" and the "within up-to-7" to guide clinical practice (63). A study by Ha et al. conducted a survival analysis and evaluation of this subclassification system with additional improvements in which B3 and B4 subclasses were merged as BIII. There are significant differences in the mOS of the three subclassifications (41.0 vs. 22.1 vs. 16.6 months, $p \leq 0.001$) (64). In 2016, Kudo et al. updated Bolondi's subclassification modified for intermediate-stage HCC (Kinki Criteria). This subclassification divides intermediate-stage HCC into B1,B2,B3 mainly based on the Child-pugh score, beyond Milan and within up-to-7 (65). A subsequent study validated the Kinki Criteria and showed a statistically significant difference in mOS among the three substages (40.5 vs. 28.1 vs. 13.0 months, $p \leq 0.001$) (66). The seven-eleven criteria proposed by Hung et al. recently divided intermediate-stage HCC into low tumor burden, intermediate tumor burden, and high tumor burden. The results show that this substage has significant discriminative power for mOS in three subgroups (33.1 vs. 22.3 vs. 11.9 months, $p \leq 0.001$) (67). At present, many subclassifications of stage B HCC have been proposed, and several clinical studies have verified (68–73) (**Table 1**). The subclassification of BCLC stage B HCC is of significant value for the evaluation of patient prognosis as well as the selection of treatment protocols. Only patients who are suitable for TACE treatment can obtain the ideal survival benefit.

COMBINATION OF TACE AND TKIs

Although TACE is the standard treatment for intermediate-stage HCC, TACE is unlikely to bring long-term clinical benefits to all patients with intermediate-stage HCC. Furthermore, TACE causes the hypoxic microenvironment, leading to the upregulation of hypoxia-inducible factor-1α (HIF-1α). Increased HIF-1α then upregulates the expression of VEGF and PDGF and increases tumor angiogenesis (14, 15, 74). For intermediate-stage HCC, TACE treatment needs to be further

TABLE 1 | Some substaging systems of intermediate stage HCC.

Criteria	Reference indicators	BCLC sub-stage	Number of patiens	mOS (months)	1st treatment option	Alternative treatment
Borondi et al. (63)*	CPT score	B1	101	41.0	TACE	LT/TACE+ablation
	Beyond MC and	B2	232	22.1	TACE or TARE	Sorafenib
	within Ut7	B3	35	14.1	-	Research trials/TACE/
	ECOG	B4	98	17.2	BSC	sorafenib
						LT
Kudo et al, (65)	CPT score	B1	158	46.8	LR/Ablation/Superselective cTACE	DEB-TACE (large, C-P 7)
	Beyond MC and	B2	236	30.0	DEB-TACE(>6cm)/HAIC(>6tumors)/	B-TACE
	within Ut7	B3:B3a	31	13.2	Sorafenib (CP-A)	cTACE
		B3b			LT/ Ablation /Superselective cTACE	DEB-TACE/B-TACE/HAIC
					HAIC/Selective DEB-TACE	BSC
Hung et al. (67)	7-11	Low TB	185	33.1	–	–
		Intermediate	224	22.3		
		TB	223	11.9		
		High TB				
Yamakado et al. (68)	CPT score	B1	139	40.5	–	–
	4-of-7	B2	180	28.1		
		B3	12	13.0		
Hiroka et al. (71)	ALBI grade	B1	94	63.5	LR/RFA/TACE	–
	Beyond MC and	B2	175	38.1	RFA/TACE	
	within Ut7	B3	452	28.0	TACE/HAIC/sorafenib (CP-A)	
		B4	33	12.5	TACE/HAIC/BSC/LT	
Hu et al. (72)	CPT socre	B1	165	29.0	TACE+LR.LT/RFA	–
	Ut7	B2	671	19.0	TACE	
		B3	190	10.0	TACE+systemic therapies	
Kim et al. (73)	CPT socre	B1	410	44.8	TACE	–
	Ut11	B2	364	21.5	TACE	
	ECOG	B3	47	11.3	Sorafenib/HAIC	

*MC, Milan criteria; Ut7/Ut11, maximum tumor diameter plus tumor number less than 7/11; 7-11, the sum of maximum tumor diameter and tumor number; 4-of-7, the four tumors of 7 cm criterion; LR, liver resection; LT, liver transplantation; HAIC, hepatic artery infusion chemotherapy; BSC, best supportive care; RFA, radiofrequency ablation; *the OS date from a study by Ha et al. (64).*

optimized to improve the response rate, protect liver function, and prolong survival. TKIs can act on multiple kinase receptors to block the information transmission of tumor cells and inhibit tumor angiogenesis. TACE monotherapy often fails to bring good clinical outcomes to patients. Since TKIs came into the treatment field of HCC, the clinical researches of TACE combined with TKIs for the treatment of intermediate-stage HCC is continuously being explored and improved (**Table 2**).

Combination of TACE and Sorafenib

In phase I clinical study of TACE combined with sorafenib in the treatment of HCC, Dufour et al. confirmed that the adverse effects of the combination therapy are equivalent to those of sorafenib monotherapy. After the combination therapy, VEGF concentrations in serum decreased from 93 ng/l to 67 ng/l, and this suggests that the combined regimen may reduce the overexpression of VEGF in the blood and inhibit the recurrence and metastasis of tumors (19). The way of administration in this study may impact the outcome of the HCC patients, which uses continuous administration (i.e., dose-escalation, and without drug discontinuation post-TACE and pre-TACE). Kudo et al. reported a phase III multi-center randomized controlled study (Post-TACE) that included Korean and Japanese patients of TACE combined with sorafenib for unresectable HCC (18). Patients with an objective response after the last TACE were given oral sorafenib within 1-3 months based on their liver function. However, the final results of the Post-TACE trial showed no significant difference in time to progression (TTP) between combination and control groups, which may be related to the low therapeutic dose of sorafenib (386mg) of the combination therapy. In this study, 60% of patients have delayed administration for more than nine weeks before randomization. The peak of the VEGF concentration in the circulating blood reached on the first day after TACE (14), so the interval between sorafenib administration before and after TACE should not be too long. In the exploratory analysis of this study, it was found that Korean patients had a better TTP hazard ratio (HR, 0.38 vs. 0.94) compared with Japanese patients, which may be related to the longer median duration of sorafenib (31 weeks vs. 16 weeks).

At the same time, Llovet et al. carried out a phase II, randomized, double-blind clinical study (SPACE) (76). Sorafenib was administrated for pre-treatment 3-7 days before the first TACE in the combined therapy group to promote the normalization of tumor blood vessels. Time to untraceable progression (TTUP), as the secondary endpoint, was proposed for the first time in this study. It is defined as a nodule receiving treatment that fails to achieve objective response after at least two TACE treatments or has contraindications for chemotherapy regimens, including macrovascular invasion (VMI), extrahepatic spread (EHS), persistent ascites, and liver function Child-Pugh B grade or ECOG PS> 2 or platelet count $\leq 60\times10^9$/L. However, no statistically significant difference was observed in TTP between the combination and the monotherapy group in this study, which may be related to the restrictive definition of TTUP. Because there will be transient liver function abnormalities and blood biochemical parameters change after TACE, it may be inappropriate to be defined as disease progression at this time. In addition, the TACE procedure in this study was performed at fixed intervals. When intrahepatic lesions respond well to TACE, unnecessary repeated TACE may impair liver function or increase the side effects of sorafenib (81). Although the primary endpoint of this trial was not statistically different, the hazard ratio of time to VMI/EHS between the combined therapy group and the monotherapy group was 0.621. This exploratory trial suggests that the combination of sorafenib plus DEB-TACE was feasible in patients with intermediate-stage HCC.

Phase III clinical study (TACE-2) of TACE combined with sorafenib conducted by Meyer et al. in a European population also showed negative results (77). No significant statistical difference between the combined therapy and the monotherapy groups were found in progression-free survival (PFS) (230 vs. 235 days, p=0.94). The failure of TACE-2 may be related to the definition of disease progression. The appearance of new lesions in the liver may not be a sign of stopping TACE or sorafenib treatment and switching to other treatment methods because it is the natural characteristic of HCC. Therefore, it may not be appropriate to use RECIST 1.1 or mRECIST evaluation criteria to define HCC progression after the combined therapy.

Based on these previous studies, a multi-center, randomized controlled, phase II study (TACTICS) confirmed the benefits of combination therapy (79). This study showed that the combined therapy group and monotherapy group had a statistical difference in the primary endpoint of PFS (25.2 months vs. 13.5 months; p=0.006). The secondary endpoints of the two groups, such as TTP (26.7 vs. 16.4 months, p=0.005), time to stage progression time (22.5 months vs. 6.3 months, p=0.001), were significantly different. The most outstanding innovation of this study was that the appearance of new lesions in the liver is not defined as tumor progression. However, the results of the TACTICS study updated in the latest ASCO GI meeting showed that no statistical difference was observed between the combined therapy group and monotherapy group in the median OS (36.2 months vs. 30.8 months; p=0.40). Updated PFS between the two groups is still significantly different (22.8 months vs. 13.5 months, p=0.02) (82).

The analysis found that the follow-up anti-tumor treatment of the trial was more common in the TACE monotherapy group (76.3% vs. 58.5%), and the administration of sorafenib treatment accounted for a higher proportion in the TACE monotherapy group (50% vs. 10.6%). This result might be because patients in the combined therapy group developed resistance to sorafenib treatment after progression. This follow-up positive anti-tumor and systemic therapy (i.e., radiofrequency ablation, TACE, hepatic artery infusion chemotherapy, or other targeted and immune drugs) prolonged survival after progression, and confounded survival analysis and diluted the OS benefit of the combined therapy group. The positive results of PFS in the TACTICS could be due to several reasons. First, new lesions in the liver were not considered tumor progression, which prolonged the combination therapy time. Second, the standard of TTUP is looser than that of the SPACE study. This also prolonged the time to change other treatment methods. The median average dose of

TABLE 2 | Some researches on TACE combined with TKIs.

Trail	Trail design	Type of trail	Inclusion criteria	TACE procedure	Definition of progression	Median OS/ PFS/TTP months	The time of TKIs administration	Median medication time (weeks)	Median medication dose (mg/d)	limitations	Common AEs* (all grade/grade 3,4)	Liver toxicities (all grade/grade 3,4)
Post-TACE (18)	S+TACE vs. P+TACE 229 vs. 229	RCT, III	Child-Pugh A ECOG 0/1 BCLC B:n.a.	cTACE,1-2 times	RECICL 2004	TTP (5.4 vs. 3.7, p = 0.252)	1-3 months after TACE	17.1	386	much lower than planned median daily dose of sorafenib (386 mg).	HFSR (82%35%) Alopecia (41%/-) Rash (40%/4%) Diarrhoea (31%/6%) Hypertension (31%15%)	Elevated AST (25%/12%) Elevated ALT (21%/8%)
BRISK-TA (75)	B+TACE vs. P+TACE 57 vs. 59	RCT, III	Child-Pugh A/B ECOG 0/1 BCLC B:52%	cTACE/D-TACE, on-demand	mRECIST	OS (26.4 vs. 26.1, p =0.5280)	After TACE	24	n.a.	early closure. differences by region.	D-appetite (82%35%) Fatigue (43%/4%) hypertension (47%/14%) A-pain (31%/6%) Diarrhea (36%/7%)	Elevated AST (35%/14%) Elevated ALT (36%/10%)
SPACE (76)	S+TACE vs. P+TACE 154 vs. 153	RCT, II	Child-Pugh A ECOG 0 BCLC B:100%	DEB-TACE, on a fixed interval	mRECIST	TT P (5.6 vs. 5.5, p =0.072)	3-7 days before TACE	21	566	the restrictive definition of TTUP. DEB-TACE on a fixed interval.	A-pain (60.1%/7.8%) Diarrhea (52.9%/3.9%) HFSR (46.4%/9.2%) Fatigue (43.1%/11.1%) Fever (38.6%/0)	Elevated AST (24.8%/24.2%) Elevated ALT (17.0%/15.1%)
TACE-2 (77)	S+TACE vs. P+TACE 139 vs. 138	RCT, III	Child-Pugh A ECOG 0/1 BCLC B:n.a.	DEB-TACE on demand	RECIST1.1	PFS (7.7 vs. 7.8, p =0.94)	2-5 weeks before TACE	17	660	heterogeneity in baseline characteristics. the strict criteria for retreatment.	Fatigue (81%/19%) A-pain (60%/13%) Diarrhoea (56%/11%) Nausea (46%/1%) Rash (38%/2%)	n.a.
ORIENTAL (78)	O+TACE vs. P+TACE 363 vs. 364	RCT, III	Child-Pugh A ECOG 0/1 BCLC B:47%	cTACE, on demand	n.a.	OS (31.1 vs. 32.3, p =0.435)	3-28 days after TACE	43.6	n.a.	early termination. heterogeneity in baseline characteristics.	A-pain (71%/6%) Pyrexia (59%/<1%) D-appetite (47%/4%) Constipation (40%/<1%) Nausea (39%/<1%)	Elevated AST (50%/43%) Elevated ALT (45%/34%)
TACTICS (79)	S+TACEV vs. TACE 80 vs. 76	RCT, II	Child-Pugh A/B7 ECOG 0/1 BCLC B:55%	cTACE, on demand	Inability to TACE/TACE failure/New Lesions are not considered as progress.	PFS (36.2 vs. 30.8; p =0.40) OS (22.8 vs. 13.5, p =0.02)	2-3 weeks before TACE	38.7	355.2	small number of patients included. modified unTACEable progression.	Anaemia (64.9%/1.3%) HFSR (53.2%/5.2%) Hypertension (51.9%/ 10.4%) Malaise (26.0%/0) Fatigue (24.7%/2.6%)	Elevated AST (93.5%/28.6%) Elevated ALT (89.6%/24.7%)
Fu et al. (99)	L+TACE vs. TACE 60 vs. 60	retrospective, nRCT	Child-Pugh A/B BCLC B:55%	D-TACE, on-demand	mRECIST	n.a.	3 days after TACE	n.a.	32.9	retrospective study. patients' willing to choose the lenvatinib treatment. small sample size.	Hypertension (48.3%/ 23.3%) Bleeding** (21.7%/1.7%) Diarrhea (18.3%/0) Diarrhea (16.7%/0) Dysphonia (15.0%/0)	Elevated AST (38.3%/3.3%) Elevated ALT (23.3%/1.7%)
Guo et al. (80)	A+TACE vs. TACE 60 vs. 60	retrospective, nRCT	Child-Pugh A/B ECOG 0/1 BCLC B:44%	cTACE, on demand	mRECIST	n.a.	3-5 days after TACE	n.a.	n.a.	retrospective study. small sample size. the short follow-up time.	HFSR (47.2%/n.a) Hypertension (27.8%/n.a) Erythra (22.2%/n.a) Proteinuria (13.9%/n.a) Hypothyroidism (8.3%/n.a)	n.a

*n.a., not available; OS, overall survival; PFS, progression-free survival; TTP,tome-to-progression; L, Lenvatinib; A, anlotinib; S, sorafenib; P, placebo; O, orantinib; B, brivanib; RCT, randomized controlled trial; D-appet, decreased appetite; A-pain, abdominal pain; AST, aspartate aminotransferase; ALT, alanine aminotransferase; *Top five common AEs; **Bleeding (gingiva).*

sorafenib in this study was only 355.2mg, but the duration of the drug was long enough (38.7 weeks). As in the SPACE study, pre-treatment with 400mg sorafenib day was given before TACE to observe the patient's tolerance to the drug and promote the normalization of tumor blood vessels. However, the pre-treatment time of TACTICS was longer for 2-3 weeks. At the same time, stopping medication is conducive to preserving liver function two days before and after each TACE. Therefore, for combined therapy of intermediate-stage HCC, we should try our best to protect liver function and extend the duration of drug medications, which may be more conducive to the survival of patients than the maximum dose of the drug. Although the OS in this trial was not statistically different between the combined therapy group and monotherapy group, the patients in the combined therapy group extended the time to stage progression, which allowed the patients to stay in the intermediate stage for a longer time and obtain a better quality of life.

For intermediate-stage HCC combination therapy studies, OS may not be a suitable primary endpoint. As a critical endpoint of cancer treatment research, OS has its limitations. First, it may require an extended follow-up to obtain sufficient patient data. Moreover, PFS seems to be a surrogate primary endpoint for OS. A study by Llovet et al. showed that the threshold of PFS ≤ 6 can predict the improvement of OS in advanced HCC (83). However, the benefits of PFS in the TACTICS had not been converted into the benefits of OS. The selection of appropriate endpoints for combination therapy is a question that still needs to be addressed in future clinical trials. Once patients are defined as disease progression during combination therapy, other treatment modalities must be introduced according to the clinical guidelines. However, whether the disease progression is the failure of combination therapy or the natural tumor biology of HCC still remains ambiguous. If the latter was the case, OS data might be confounded by follow-up treatment after disease progression (84). So the definition of progression may require refinement, especially in the combination therapy of the intermediate-stage HCC. The definition of disease progression affects TACE and sorafenib's performance, thereby affecting the endpoints of the trial analysis. At present, more and more interventional physicians are beginning to consider that the appearance of new lesions in the liver cannot be counted as progress.

Combination of TACE and Brivanib

Park et al. confirmed the efficacy of brivanib for advanced HCC (85). The study included 55 patients with unresectable, advanced, or locally metastatic HCC. Studies have confirmed that brivanib and sorafenib are equally effective in treating advanced HCC. The HCC patients is well tolerated with brivanib. Based on this phase II study results, Kudo et al. investigated brivanib as an adjuvant combination therapy for TACE (75). This randomized, double-blind, placebo-controlled phase III clinical study (BRISK-TA) enrolled a total of 870 HCC patients who met TACE criteria. After the first TACE, they were randomly assigned (1:1), and 800mg of brivanib and placebo were taken each day orally. The administration of brivanib in the study varied from 2 to 21 days after TACE according to liver function. There was no statistically significant difference in OS between the combined therapy and monotherapy groups (26.4 months vs. 26.1 months, p=0.5280).

Regarding the negative results of this study, Kudo et al. consider that the trial only recruited 502 patients due to early termination, which is less than the planned 870 patients (81). Although no positive results were observed in mOS, there were statistical differences between time to extrahepatic spread (TTES)/ time to vascular invasion (TTVI) and objective response rate. The number of TACE procedures in the combined therapy group is also less than in the monotherapy group. All these indicated that TACE combined with brivanib has a positive anti-cancer effect.

Combination of TACE and Orantinib

Orantinib is a multi-targeted, orally active, small-molecule tyrosine kinase inhibitor (TKI) that inhibits the VEGF-2 and the PDGF-β receptor (86, 87). Many clinical trials have confirmed the safety and effectiveness of orantinib in treating advanced HCC. In the study by Inaba et al., patients treated with TACE monotherapy were randomly divided into orantinib and no medication groups (88). A total of 103 patients were included in the study. The results showed that the median PFS of the combined therapy group and monotherapy group were 157 and 122 days, respectively. Although there was no statistical difference between the two groups, the mPFS of the combination group had a significant prolongation trend. It is necessary to test the combination of TACE and orantinib further. Kudo et al. explored the efficacy of TACE combined with orantinib in a randomized, double-blind, placebo-controlled, multi-center multi-center, phase III study (ORIENTAL) (78). A total of 889 patients were enrolled in this study. These patients were randomly assigned to the combined therapy and monotherapy groups at a 1:1 ratio. Orantinib administration was given 200mg orally twice a day and 3-28 days after TACE according to whether the patients met the criteria for administration. There was no statistically significant difference in mOS between the combination and control groups (31.1 months vs. 32.3 months, p=0.5280). In the subgroup analysis, it was found that Japanese patients observed a trend toward improved mOS compared with the control group. This could be due to better medication dosages control in Japanese patients. About 50% of Japanese patients had reduced their medication dosages, while only 25% of patients in Korea and Taiwan have reduced their dose. A timely reducing drug dose may decrease drug toxic side effects, affecting patients' treatment and prognosis.

Combination of TACE and Anotinib

A phase III randomized clinical study confirmed that anlotinib has survival benefits for non-small cell lung cancer (89). The mechanism action of anlotinib may be through the Erk and Akt pathways to inhibit HCC proliferation, suppress tumor growth, and induce tumor apoptosis (90–92). A retrospective study compared TACE combined with anlotinib and TACE monotherapy to treat intermediate-stage HCC (80). The study included 82 patients with unresectable HCC. Patients in the combined therapy group (n=36) took orally anlotinib 12 mg daily for 3-5 days after the first TACE (taken for two weeks and

stopped for one week). The results demonstrated a significant difference in PFS (7.35 months vs. 5.54 months, p=0.035). Although no statistical difference was observed in the 3-month survival rate (97.2% vs. 93.5%, p=0.627), the 6-month and 1-year survival rate of the combined therapy group (83.3% vs. 56.5%, p=0.016; 66.7% vs. 19.6%, p = 0.016) are significantly higher than monotherapy group. Meanwhile, no grade 4 adverse events were observed in the two groups of patients, and all the adverse events were alleviated after treatment or dose adjustment. The follow-up durations in this study were relatively short. Whether the benefit of PFS translates into OS benefit is still unclear. Further researches, preferably with large clinical studies, are needed to confirm the clinical effect of TACE combined with anlotinib.

Combination of TACE and Lenvatinib

Lenvatinib is a novel oral multi-kinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, platelet-derived growth factor (PDGF) receptor-alpha, rearranged during transfection (RET), and KIT (93–97). Recently, an open-label, multi-center phase III clinical randomized non-inferiority study (REFLECT) compared the efficacy of lenvatinib and sorafenib in patients with advanced HCC (98). The results demonstrated that most of the lenvatinib group was comparable to that of the sorafenib group. A recent retrospective study compared TACE combined with lenvatinib with TACE monotherapy to treat unresectable HCC (99). This study included 120 patients with unresectable HCC. Patients in the combination group took lenvatinib orally three days after TACE treatment and withdrew the drug three days before repeating on-demand TACE treatment. The dose of lenvatinib is mainly determined according to the weight of patients. Patients (bodyweight≥60kg) take 12mg, and patients (bodyweight<60kg) take 8mg. The final results showed that the combined therapy group's 1-year and 2-year OS (88.4% and 79.8%) were higher than the control group's (79.2% and 49.2%, P =0.047). In terms of PFS, the combination group was also better than the control group (1 year: 78.4% vs. 64.7%; 2 years: 45.5% vs. 38.0%, p<0.001). The combined therapy group also had a better objective response rate (68.3% vs. 31.7%, p<0.001). Meanwhile, the patients in the combined therapy group tolerated lenvatinib well. This study is the first retrospective study of TACE combined with lenvatinib in treating unresectable HCC. Although the results showed that the combined therapy group tends to prolong the OS and PFS, the median follow-up time of the combined therapy group and the control group is only 11.6 months and 17.5 months, respectively. The proportion of treatment in the combined group after disease progression is relatively lower (35.7% vs. 62.2%). The final results of OS and PFS is still unclear. In this study, the TACE treatment interval of the combined group was significantly longer than that of the control group (103.3vs.74.7d, p=0.004), which provided the possibility to protect the liver function of the patients. Therefore, the clinical efficacy of TACE combined with lenvatinib in patients may require further large-scale randomized controlled clinical studies to verify.

WHAT ELSE CAN WE DO?

The treatment of intermediate-stage HCC has always been a hotly debated topic. The emergence of molecule-targeted drugs has provided more treatment options for intermediate-stage HCC with TACE as the main therapeutic modality. With the emergence and update of various new drugs, researcher's attention and the pursuit of treatment effect for intermediate-stage HCC have also increased. The treatment goal of intermediate-stage HCC has gradually expanded from delaying disease progression to achieving tumour downstaging and undergoing curative conversion therapy. In the future, the exploration of treatment strategies for intermediate-stage HCC should focus on the prolongation of OS and the curative conversion therapy after tumour downstaging.

The advent of immune checkpoint inhibitors (ICIs) may provide new directions for the combination treatment of HCC. Previous studies (e.g., KEYNOTE-224 and KEYNOTE-240) have confirmed that pembrolizumab has favorable disease control and side effects for HCC patients previously treated with sorafenib (100, 101). Recently, significant progress has been achieved in a global, open-label, phase 3 trial (IMBRAVE 150). This study compared the clinical efficacy of atezolizumab (anti-PDL1 checkpoint inhibitor) plus bevacizumab(anti-VEGF) and sorafenib for unresectable HCC. Results of the study demonstrated that the mPFS of patients in the atezolizumab–bevacizumab group was significantly longer than that in the sorafenib group (6.8 vs. 4.3 months, <0.001) (102). In the latest ASCO GI 2021 meeting, the result showed that mOS was significantly longer in the atezolizumab–bevacizumab group than in the sorafenib group (19.2 vs. 13.4 months, <0.001). Therefore, in the 2022 updated BCLC strategy, the atezolizumab–bevacizumab therapy is recommended as the first-line treatment for advanced HCC (13). It is not difficult to see that the update of the treatment strategy for advanced HCC will bring more survival benefits to patients and affect the treatment strategy of intermediate-stage HCC. The earlier application of TKIs and their combination with TACE in intermediate-stage HCC could make it possible to reduce the number of TACE treatments, maximize the protection of liver function, and ultimately prolong the overall survival of patients with HCC.

Some studies of TACE combined with ICIs are on the way, and it is unclear whether this combination is beneficial for intermediate-stage HCC. However, a retrospective study by Zheng et al. demonstrated the safety and efficacy of TACE combined with sorafenib plus immune checkpoint inhibitors (TACE+Sor+ICIs) (103). This study included 51 patients with intermediate and advanced TACE-resistant HCC, divided into TACE+Sor+ICIs and TACE combined with sorafenib (TACE+Sor) groups. The results showed that the disease control rate of the TACE+Sor+ICIs group was significantly higher than that of the TACE+Sor group (81.82 vs. 55.17%, P = 0.046). Besides, they observed that the mPFS (16.26 vs. 7.30 months, P < 0.001) and mOS (23.3 vs. 13.8 months, P = 0.012) of the TACE+Sor+ICIs group was significantly longer than that of the TACE+Sor group. Another study also confirmed that for intermediate and

advanced HCC, tumors in the TACE with molecular targeted agents (MTGs) plus immune checkpoint inhibitors (ICIs) group had a higher liquefactive necrosis rate than tumors in the TACE with MTGs group (30% vs. 4.8%, P=0.006) (104). If TACE is combined with TKIs plus ICIs in treating patients with intermediate-stage HCC, is it possible to acquire better clinical efficacy? This needs to be confirmed by further large clinical studies.

Based on the outcomes of REFLECT, lenvatinib is now approved for the first-line treatment of advanced HCC. In the REFLECT study, masked independent imaging review confirmed a significantly higher objective response rate in the lenvatinib arm than in the sorafenib arm by mRECIST (40.6 vs 12.4%, p<0.0001) (98). Previous studies have shown that ORR and sustained response duration are effective predictors of longer OS, and early treatment response remains a reliable predictor of a good prognosis (23, 24). At present, studies have explored how to translate the high objective response rate of lenvatinib into more prolonged survival in patients with intermediate-stage liver cancer. A study conducted by Kudo et al. demonstrated that lenvatinib has higher ORR (73.3% vs. 33.3%, p<0.001) and mOS (37.9 vs. 21.3 months, p<0.01) as first-line versus TACE for intermediate-stage HCC beyond up-to-seven Criteria and child-pugh A liver function (59). Another study investigated lenvatinib-TACE sequential therapy versus lenvatinib alone in patients with intermediate-stage HCC who were not unsuitable for TACE. The results showed that the OS of the combined treatment group was significantly longer than that of the lenvatinib group (not reached vs. 16.9 months, p = 0.007) (105). Two studies suggest that early lenvatinib-TACE sequential therapy may be a good combination therapy for patients with intermediate-stage HCC who are not suitable for TACE. Not just the ongoing TACTICS-Lenvatinib study, more randomized controlled trials are needed to confirm the clinical benefit of this combination in the intermediate-stage HCC. Not only that, but the high objective response rate of lenvatinib will also provide more opportunities for the transformation therapy of intermediate-stage HCC. It can be seen that lenvatinib has shown a trend of replacing other TKI drugs in the combined treatment of intermediate-stage HCC.

The extensive randomized controlled clinical studies of TACE combined with TKIs in the treatment of intermediate-stage HCC have all failed. In the future, the treatment of the intermediate-stage HCC remains challenging. The etiology of HCC gradually changes, and non-viral hepatitis caused by NAFLD and NASH increases. This may also change the holistic treatment concept of HCC in the future. It can be found that the combined treatment has survival benefits in specific subgroups of HCC patients. Therefore, substaging and guidelines for stage B HCC require more refined definitions. The combination treatment regimen for HCC patients should be individualized based on individual patient factors. The selection of the patient population for combination therapy will be very worthy of attention in the future. On the other hand, TKIs combined with more embolization treatments including cTACE, DEB-TACE and TARE need to be explored. At the same time, the efficiency improvement of TACE combined with TKIs might ultimately be implemented by improvement of embolization efficacy and technical limitations of TACE, preservation of liver function and management of adverse events. Several clinical trials are currently underway to explore the efficacy of combination therapy for intermediate-stage HCC. Therefore, better results can be expected in the future.

In conclusion, the road of combined therapy for intermediate-stage HCC is not smooth. However, combined therapy is an inevitable trend for the future development of HCC. It is believed that more optimized combination methods will bring more excellent clinical effects soon.

AUTHOR CONTRIBUTIONS

JD and FW wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Efficacy and safety of camrelizumab plus transarterial chemoembolization in intermediate to advanced hepatocellular carcinoma patients: A prospective, multi-center, real-world study

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Objective: Camrelizumab is a newly developed program-death receptor one inhibitor; the real-world evidence about its application in hepatocellular carcinoma (HCC) treatment is lacking. Therefore, this prospective, multi-center, real-world study evaluated the efficacy and safety of camrelizumab plus transarterial chemoembolization (TACE) in treating intermediate-to-advanced HCC patients.

Methods: This study consecutively enrolled 101 intermediate to advanced HCC patients. All patients received camrelizumab-based treatment within 30 days of the perioperative period of the TACE operation. The primary outcome was progression-free survival (PFS), and the secondary effects were overall survival (OS), objective response rate (ORR), disease control rate (DCR), and AEs.

Results: Specifically, the median PFS was 9.7 (95% confidence interval: 7.4–12.0) months, with a 1-year PFS rate of 30.6%. Meanwhile, the median OS was not reached (NR) yet, with a 1-year OS rate of 61.9%. Besides, the CR, PR, SD,

and PD rates were 12.8%, 44.9%, 29.5%, and 12.8%, respectively. The ORR and DCR were 57.7% and 87.2%, respectively. More cycles of camrelizumab were independently correlated with prolonged PFS (hazard ratio (HR): 0.415, P = 0.002), whereas longer intervals between camrelizumab administration and TACE were independently associated with unfavorable PFS (HR: 1.873, P = 0.032). The incidence of total AEs was 90.1%; most AEs were grade 1 (20.8%), grade 2 (28.7%) and grade 3 (37.6%), while only 3 (3.0%) patients had grade 4 AEs.

Conclusion: The camrelizumab plus TACE regimen is effective and safe, indicating its potential to serve as a promising treatment choice for intermediate to advanced HCC patients.

KEYWORDS

camrelizumab, transarterial chemoembolization, hepatocellular carcinoma, survival, adverse event

Introduction

Hepatocellular carcinoma (HCC), one of the most common solid tumors, is the second leading cause of cancer-related deaths globally, with an estimated 830,180 new deaths in 2020 (1). Among these, about half of the HCC patients are derived from China. Meanwhile, more than 50% are diagnosed with intermediate to advanced HCC (2–5). Transarterial chemoembolization (TACE) is recommended for HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage B who are not suitable for surgical resection, according to the guidelines issued by the American Association for the Study of Liver Diseases (AASLD) in 2018 (6). On the other hand, according to the Primary Liver Cancer Guidelines (2017 Edition) published in China, the TACE-based regimen is the primary treatment modality for HCC patients with China liver cancer (CNLC) stage IIb–IIIa (7). Even though TACE is one of the most common non-surgical treatments for patients with intermediate to advanced HCC, it can still lead to a post-therapy neoangiogenetic reaction or induce incomplete embolism, which further results in an unsatisfactory survival profile (7–9). Thus, exploring novel treatment choices in these patients should be highly prioritized.

Recently, TACE combined with other treatment modalities (including TACE plus tyrosine kinase inhibitors (TKIs) and TACE plus program-death receptor 1 (PD-1) inhibitor) is gradually becoming the primary regimen for patients with intermediate to advanced HCC, which has shown a good efficacy profile (10, 11). For instance, one study showed that TACE plus apatinib discloses a higher OS than TACE only in advanced HCC patients with macroscopic vascular invasion (median OS: 18.2 months vs. 8.5 months) (10). Another study indicated that TACE plus PD-1 inhibitor achieved an acceptable efficacy profile with a partial response (PR) of 22%, a stable disease (SD) of 78%, a 12-month progression-free survival (PFS) rate of 40%, and a 12-month overall survival (OS) rate of 71% (11). However, most of these studies are either single-armed or randomized controlled studies. In contrast, real-world studies remain rare, which might be more likely to reflect the actual clinical circumstances.

Camrelizumab, a PD-1 inhibitor, was independently developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. in China and has recently been approved by the Chinese Food and Drug Administration (CFDA) to treat hepatocellular carcinoma. A few studies have exhibited the efficacy of camrelizumab in patients with advanced HCC (12–14). For instance, a study disclosed that a combination of camrelizumab with sorafenib, TACE, and radiotherapy in treating advanced HCC patients with portal vein tumor thrombus achieved a median PFS of 15.7 months and a 1-year OS of 83.3% (12). Another study demonstrated that camrelizumab plus lenvatinib had a median PFS of 8.0 months in advanced HCC patients, which is higher than patients who received lenvatinib only (13). However, the sample size of these studies is relatively small. Besides, recent studies on the efficacy and safety of TACE plus camrelizumab in treating intermediate-to-advanced HCC patients are scarce.

Therefore, we conducted a prospective, real-world study with a large sample size (including 101 patients with intermediate to advanced HCC) and evaluated the efficacy and safety of camrelizumab plus TACE for treating patients with intermediate to advanced HCC.

Methods

Patients

This was a prospective, open-label, multi-center, single-armed, and observational real-world study. The study consecutively screened 101 intermediate to advanced HCC from 173 patients treated with camrelizumab plus TACE in 36 medical centers between August 2019 and March 2021. Patients who met the following conditions were eligible for enrollment: (i) diagnosis of primary HCC in line with Primary Liver Cancer Guidelines (2017 Edition) (7); (ii) over 18 years of age; (iii) BCLC stage B or C according to the criteria of 2018 version; (iv) with at least one measurable lesion as the target lesion revealed by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria (15); (v) suitable for treatment with camrelizumab plus TACE; (vi) without serious abnormal blood, heart, lung, liver, or kidney function; and (vii) volunteered to participate in the study and willing to be followed up regularly. The patients with the following conditions were excluded: (i) had a contraindication to camrelizumab (an allergy to the active ingredient and excipients of camrelizumab). In detail, the active ingredient included camrelizumab (humanized anti-PD-1 monoclonal antibody); the excipients included, α, α-dihydrate trehalose, polysorbate 20, glacial acetic acid, sodium hydroxide, and water for injection); (ii) history of immunodeficiency disease or organ transplantation; (iii) concomitant with other cancers or malignancies; and (iv) pregnant or lactating women. The Institutional Review Board approved the current study with the approval number ChiECRCT20190186. All eligible patients provided written informed consent. This study was registered on the Chinese Clinical Trial Registry (available at: http://www.chictr.org.cn/) with the registration number ChiCTR1900026163.

Treatment procedures

After enrollment, all patients received camrelizumab-based treatment within 30 days of the perioperative period of the TACE operation. The TACE operation was performed as described in a previous study (16). After identifying the tumor-feeding artery by visceral angiography, the microcatheter was catheterized by the distal super-selective method. Then, the chemotherapy drug solution of epirubicin mixed with lipiodol was slowly injected, followed by embolization using polyvinyl alcohol particles or gelatin sponge particles. The embolization ended when the contrast agent stagnated. During 30 days of the perioperative period of the TACE operation, camrelizumab was administered by intravenous drip at a dose of 200 mg for 30 min (between 20 and 60 min) each cycle, and every 2 weeks (Q2W) or every 3 weeks (Q3W) was a treatment cycle. Based on camrelizumab treatment, TKIs such as apatinib, lenvatinib, sorafenib, regorafenib, and anlotinib were also allowed for combination treatment. For the use of apatinib, it was recommended to stop the administration 4 to 7 days before TACE and start it on the day of the initiation of camrelizumab. Apatinib was administered orally at a dose of 250 mg daily. The camrelizumab-based treatment was continuously administered until the physicians determined that patients would not benefit from it anymore, the maximum duration of which was 2 years. Besides, the cycle of camrelizumab alone was also recorded, named as "cycles of camrelizumab."

Follow-up

The contrast-enhanced CT or MRI was examined at baseline and week 4 after the initiation of the treatment, then performed every 8 weeks, based on which the treatment response was assessed according to the mRECIST criteria (15), including complete response (CR), PR, SD, and progressive disease (PD). Adverse events (AEs) were closely monitored during the treatment, and the monitoring was continued up to the 28th day after the last administration of camrelizumab. The response was evaluated by the best overall response using the mRECIST criteria. Survival follow-up was performed monthly until the death of patients lost to follow-up or the end of the study, whichever came first, during which phone calls collected the survival data from all patients, their families, or local physicians, and the last date of follow-up was 1 July 2021.

Outcome assessment

The primary outcome was PFS; the secondary effects were OS, objective response rate (ORR), disease control rate (DCR), and AEs. PFS was defined as the duration from the admission to the disease progression or death of patients, whichever came first; OS was defined as the duration from the enrollment to the death of the patient. The ORR was defined as the percentage of patients with CR or PR as the best response status; DCR was expressed as the percentage of patients with CR, PR, or SD as the best response status. The AEs were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 (17). Besides, data from patients with TACE treatment history were also extracted. These patients were classified as TACE refractory and not TACE refractory according to the criteria submitted by the Japan Society of Hepatology (18).

Statistical analysis

SPSS 26.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism 7.01 (GraphPad Software Inc., San Diego,

California, USA) were used for data analysis and figure construction, respectively. All 101 patients were included in the safety analysis, and 78 patients who underwent the same imaging examination (CT or MRI) as the baseline throughout the assessment process were included in the efficacy and survival analysis. Continuous data were presented as mean with standard deviation (SD), and categorial data were expressed as counts (percentage). Comparison between groups was evaluated by the chi-square test and Fisher's exact test. The Kaplan–Meier method and log-rank test were applied to determine the difference in PFS/OS between groups. A Cox's proportional hazard regression analysis was carried out for prognostic factor analysis, and a hazard ratio with a 95% confidence interval (CI) was shown. All significant variables (P <0.1 in univariate Cox's regression analysis) were included in multivariate Cox's regression for independent prognostic factor analysis. Statistical significance was derived if the two-sided P-value was less than 0.05.

Results

Study flow

Among the 173 HCC patients screened, 44 were excluded from this study because they did not meet the inclusion criteria; the remaining 129 patients were included. During the following treatment period, 28 patients were excluded for violating the study protocol. Subsequently, data from 101 patients were included in the analysis. Of these, the imaging results before and after treatment were inconsistent in 17 patients. Furthermore, imaging results from six patients were evaluated only at baseline but not after the treatment. Therefore, the efficacy and survival analysis excluded these 23 patients without eligible imaging assessment. Consequently, only 78 patients were included in the efficacy and survival analysis, and all 101 patients were included in the safety analysis. The detailed study flow is displayed in Figure 1.

Clinical characteristics

The mean age of 101 enrolled HCC patients was 56.8 ± 11.2 years (Table 1), of whom 12 (11.9%) were females and 89 (88.1%) were males. In terms of the disease characteristics, 75 (74.3%) patients presented with hepatitis B virus positive; 1 (1.0%), 16 (15.8%), 26 (25.8%), and 56 (55.4%) patients exhibited CNLC stages of Ib, IIa, IIb, IIIa, and IIIb, respectively, while the CNLC stage of 1 (1.0%) patient was unknown (UK). Regarding the treatment history: 29 (28.7%) patients had never experienced TACE treatment before, while 32 (31.7%), 16 (15.8%), 7 (6.9%), and 17 (16.8%) patients had 1, 2, and 3, and more than three times of previous TACE treatments,

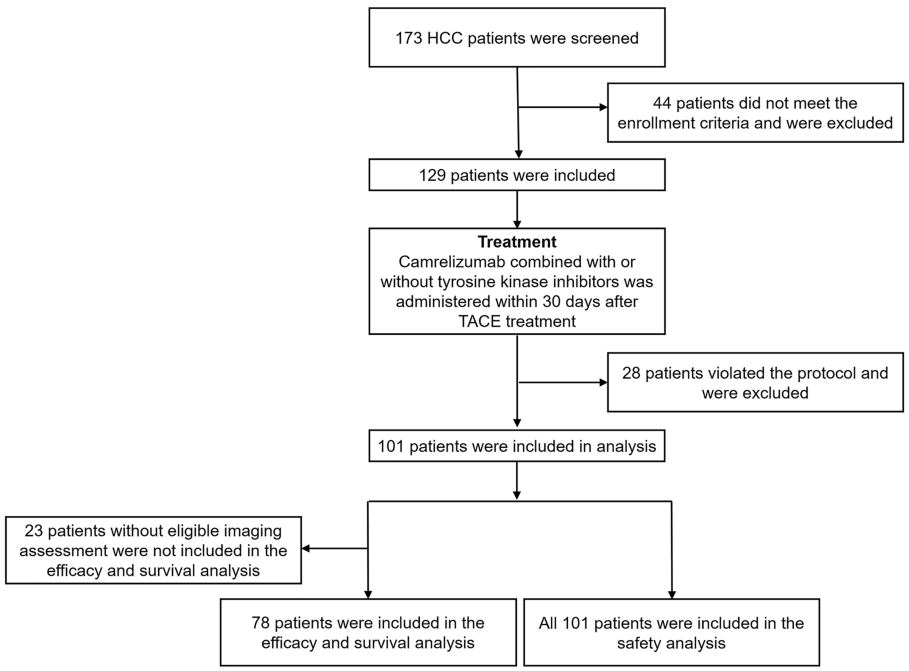

FIGURE 1
Study flow. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

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Table 1 Clinical characteristics.

Items	HCC patients (N = 101)
Demographic characteristics	
Age (years), mean ± SD	56.8 ± 11.2
Gender, No. (%)	
Female	12 (11.9)
Male	89 (88.1)
Disease characteristics	
HBV, No. (%)	75 (74.3)
ECOG PS score, No. (%)	
0	26 (25.7)
1	74 (73.3)
2	1 (1.0)
Child–Pugh class, No. (%)	
A	72 (71.3)
B	29 (28.7)
Extrahepatic metastasis, No. (%)	56 (55.4)
Vascular invasion, No. (%)	42 (41.6)
BCLC stage, No. (%)	
B	29 (28.7)
C	72 (71.3)
CNLC stage, No. (%)	
Ib	1 (1.0)
IIa	1 (1.0)
IIb	16 (15.8)
IIIa	26 (25.8)
IIIb	56 (55.4)
UK	1 (1.0)
AFP (ng/ml), No. (%)	
<400	57 (56.4)
≥400	39 (38.6)
UK	5 (5.0)
Treatment history	
Hepatectomy, No. (%)	27 (26.7)
Times of previous TACE, No. (%)	
0	29 (28.7)
1	32 (31.7)
2	16 (15.8)
3	7 (6.9)
>3	17 (16.8)
Refectory to TACE in patients with TACE treatment history, No. (%)	
No	26 (25.7)
Yes	31 (30.7)
Previous treatment lines, No. (%)	
First-line	82 (81.2)
Second-line	17 (16.8)
> Second-line	2 (2.0)
Treatment in the study	
Times of TACE, No. (%)	
≤3	88 (87.1)
>3	13 (12.9)

(Continued)

Continued

Items	HCC patients (N = 101)
Timing of camrelizumab administration, No. (%)	
Before TACE	9 (8.9)
After TACE	92 (91.1)
Treatment cycle of camrelizumab	
Q2W	2 (2.0)
Q3W	99 (98.0)
Cycles of camrelizumab, No. (%)	
≤2	12 (11.9)
3–4	33 (32.7)
>4	56 (55.4)
Interval between TACE and camrelizumab administration, No. (%)	
Within 7 days	84 (83.2)
Within 8 to 14 days	9 (8.9)
Within 15 to 28 days	8 (7.9)
Treatment regimen, No. (%)	
Monotherapy of camrelizumab	53 (52.5)
Combination therapy with TKI	48 (47.5)
Apatinib	27 (26.7)
Lenvatinib	10 (9.9)
Sorafenib	4 (4.0)
Anlotinib	4 (4.0)
Regorafenib	3 (3.0)

HCC, hepatocellular carcinoma; SD, standard deviation; HBV, hepatitis B virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer; UK, unknown; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization; Q2W, every 2 weeks; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitors.

respectively. Becauseof the current treatment in this study: 9 (8.9%) patients were administered with camrelizumab before TACE, whereas 92 (91.1%) patients received camrelizumab after TACE; Two (2.0%) patients received camrelizumab treatment every 2 weeks (Q2W), whereas 99 (98.0%) patients received camrelizumab treatment every 3 weeks (Q3W). Additionally, 84 (83.2%) patients were administered with camrelizumab within 7 days of the perioperative period of the TACE operation; nine (8.9%) patients received camrelizumab treatment within 8 to 14 days of the perioperative period of the TACE operation; and eight (7.9%) patients were treated with camrelizumab within 15 to 28 days of the perioperative period of the TACE operation. Furthermore, 48 (47.5%) patients received combination therapy with tyrosine kinase inhibitors (TKI), whereas 53 (52.5%) patients did not. Meanwhile, the most commonly used TKI was apatinib (26.7%), followed by lenvatinib (9.9%), sorafenib (4.0%), anlotinib (4.0%), and regorafenib (3.0%). Other detailed clinical characteristics are exhibited in Table 1.

Clinical response

Specifically, 10 (12.8%) and 35 (44.9%) patients achieved CR and PR, respectively (Figure 2A). Besides, 23 (29.5%) patients retained SD, while 10 (12.8%) patients got PD. Thus, the ORR and DCR were 57.7% and 87.2%, separately (Figure 2B). Subgroup analysis disclosed that elevated cycles of camrelizumab were correlated with increased ORR (P = 0.023), while other clinical characteristics were not associated with the ORR or DCR (all P >0.050, Table 2). Additionally, images of two patients who achieved PR after the combination treatment were also shown (Supplementary Figures 1, 2).

Survival profiles

The median PFS was 9.7 (95% CI: 7.4–12.0) months, with a 1-year PFS rate of 30.6% (Figure 3A); Besides, the median OS was not yet reached (NR), with a 1-year OS rate of 61.9% (Figure 3B).

Subgroup analysis of PFS revealed that higher cycles of camrelizumab were associated with the favorable PFS (hazard ratio (HR): 0.503, 95% CI: 0.320–0.792, P = 0.003, Table 3); a longer interval between camrelizumab administration and TACE was related to the unfavorable PFS (HR: 1.702, 95% CI: 1.039–2.790, P = 0.035), whereas other clinical characteristics were not associated with the PFS (all P >0.05). In terms of the subgroup analysis of OS, it revealed that the presence of vascular

invasion (HR: 4.152, 95% CI: 1.476–11.680, P = 0.007), more times of previous TACE (HR: 1.537, 95% CI: 1.110–2.149, P = 0.012) and a longer interval between camrelizumab administration and TACE (HR: 2.542, 95% CI: 1.398–4.620, P = 0.002) were associated with declined OS, whereas higher cycles of camrelizumab were associated with favorable OS (HR: 0.401, 95% CI: 0.221–0.729, P = 0.003).

Based on the findings from the subgroup analysis of PFS and OS, the association of the interval between camrelizumab administration and TACE with survival was subsequently determined by KM curve and log-rank tests, which indicated that the interval between camrelizumab administration and TACE was not correlated with PFS (P = 0.078, Figure 4A). However, the OS of those patients with a different interval between camrelizumab administration and TACE was varied (P = 0.001, Figure 4B). In detail, patients with camrelizumab administration within 15 to 28 days of the perioperative period of the TACE operation had the lowest accumulating OS rate, followed by those with camrelizumab administration within 8 to 14 days of the perioperative period of the TACE operation, and the highest in those with camrelizumab administration within 7 days of the perioperative period of the TACE operation. Apart from that, the baseline features between patients who were with and without TACE refractory were also compared; their baseline features were almost the same, except that the AFP level was higher in HCC patients without refractory to the TACE treatment (P = 0.038, Supplementary Table 1). However, the ORR (P = 0.610, Supplementary Figure 3A), PFS (P = 0.809, Supplementary Figure 3B), and OS (P = 0.250, Supplementary Figure 3C) were similar between these two groups.

Independent factors predicting the survival

To evaluate the independent factors predicting PFS and OS, the multivariate Cox's proportional hazards regression analysis was performed, which displayed that more cycles of camrelizumab were an independent factor in predicting the longer PFS (HR: 0.645, 95% CI: 0.243–1.708, P = 0.002), whereas a longer interval between camrelizumab administration and TACE was independently associated with pejorative PFS (HR: 1.873, 95% CI: 1.506–3.322, P = 0.032, Table 4). Additionally, the presence of vascular invasion (HR: 9.030, 95% CI: 2.355–34.629, P = 0.001), more times of previous TACE (HR: 1.618, 95% CI: 1.088–2.407, P = 0.018) were independent factors in predicting unfavorable OS.

AEs

The incidence of total AEs was 90.1%. Besides, most AEs were grade 1 (20.8%), grade 2 (28.7%), and grade 3 (37.6%), while only three (3.0%) patients caused grade 4 AEs (Table 5). Concerning the hematologic AEs, the overall incidence was 90.1% and the most common hematologic AEs included transaminase elevation (60.4%), thrombocytopenia (57.4%), hypoalbuminemia (54.5%), hyperbilirubinemia (47.5%), leukopenia (42.6%), neutropenia (40.6%), anemia (39.6%), albuminuria (26.7%), and creatinine elevation (3.0%). Regarding the non-hematologic AEs, with an overall incidence of 28.7%, and the most common non-hematologic AEs were immune-related AEs (7.9%), rash (6.9%), reactive cutaneous capillary endothelial proliferation (RCCEP) (5.9%), fever (5.0%), pain (5.0%), fatigue (5.0%), loss of appetite (4.0%), hand-foot syndrome (1.0%), as well as nausea and vomiting (1.0%).

Discussion

TACE has been shown to have anti-tumor efficacy. It is recognized as one of the most common nonsurgical treatments for patients with intermediate to advanced HCC. At the same time, it might simultaneously lead to the post-therapy neoangiogenetic reaction or induce hypoxia, which further leads to increased expression of programmed death-1 ligand (PD-L1); survival of HCC patients is still undesirable (7–9, 19, 20). For instance, one study indicated that TACE might upregulate the pro-inflammatory pathways; meanwhile, it was associated with the low intratumoral density of immune-exhausted effector cytotoxic and Tregs and further regulated the microenvironment of HCC (20). Another study exhibited that TACE might be involved in regulating post-therapy neoangiogenetic reactions *via* altering VEGF expression in HCC patients (21). The emergence of novel drugs such as PD-1 inhibitors mechanically leads to the possibility of combination therapy with TACE, whose combination has shown a certain efficacy in patients with HCC (11). Thus, to investigate the efficacy of TACE plus PD-1 inhibitor in HCC patients in a real-world study, we conducted a prospective, real-world study with a large sample size (including 101 patients with intermediate to advanced HCC). Meanwhile, all patients received camrelizumab-based treatment within 30 days of the TACE operation. We found that: 1) the ORR and DCR were 57.7% and 87.2%, respectively. In addition, the median PFS was 9.7 months, and the OS was NR; 2) the presence of vascular invasion was not associated with the ORR, DCR, or PFS, whereas it correlated with unfavorable OS; the longer interval between camrelizumab administration and TACE was related to the unsatisfying OS; more cycles of camrelizumab correlated with satisfying PFS and OS; the timing of camrelizumab administration (before and after TACE) was not associated with the PFS and OS; and 3) the safety profile of patients with advanced HCC treated with camrelizumab plus TACE was acceptable and manageable.

Of note is the population in this study: Differing from the etiopathology of other countries in the world, the prevalence of

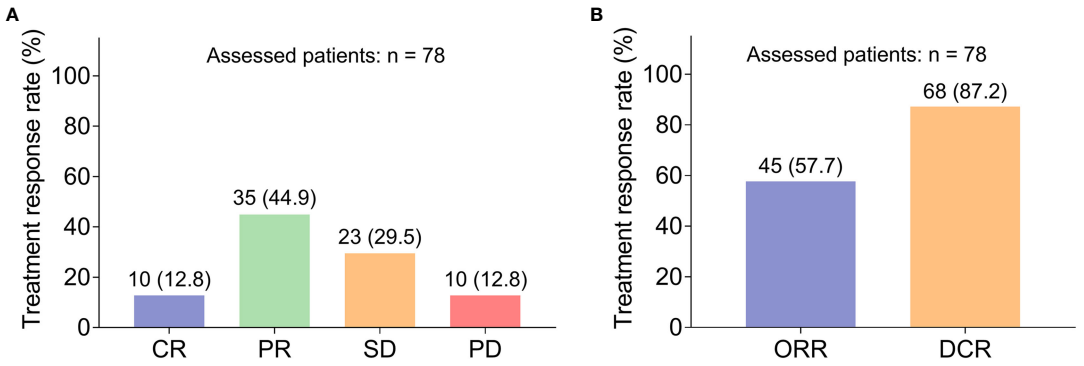

FIGURE 2
Treatment response. The CR, PR, SD, and PD rates in HCC patients receiving camrelizumab plus TACE **(A)**; The ORR and DCR rates in HCC patients receiving camrelizumab plus TACE **(B)**. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

TABLE 2 Subgroup analysis of clinical response.

Items, No. (%)	ORR	Non-ORR	*P*-value	DCR	Non-DCR	*P*-value
Age			0.963			0.680
≤65 years	37 (57.8)	27 (42.2)		55 (85.9)	9 (14.1)	
>65 years	8 (57.1)	6 (42.9)		13 (92.9)	1 (7.1)	
Gender			1.000			1.000
Female	4 (57.1)	3 (42.9)		6 (85.7)	1 (14.3)	
Male	41 (57.7)	30 (42.3)		62 (87.3)	9 (12.7)	
HBV			0.224			0.107
No	12 (70.6)	5 (29.4)		17 (100.0)	0 (0.0)	
Yes	33 (54.1)	28 (45.9)		51 (83.6)	10 (16.4)	
ECOG PS score			0.673			0.348
0	13 (59.1)	9 (40.9)		21 (95.5)	1 (4.5)	
1	31 (56.4)	24 (43.6)		46 (83.6)	9 (16.4)	
2	1 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Child–Pugh class			0.608			1.000
A	35 (59.3)	24 (40.7)		51 (86.4)	8 (13.6)	
B	10 (52.6)	9 (47.4)		17 (89.5)	2 (10.5)	
Extrahepatic metastasis			0.522			0.172
No	21 (61.8)	13 (38.2)		32 (94.1)	2 (5.9)	
Yes	24 (54.5)	20 (45.5)		36 (81.8)	8 (18.2)	
Vascular invasion			0.630			0.086
No	27 (60.0)	18 (40.0)		42 (93.3)	3 (6.7)	
Yes	18 (54.5)	15 (45.5)		26 (78.8)	7 (21.2)	
BCLC stage			0.777			0.155
B	15 (60.0)	10 (40.0)		24 (96.0)	1 (4.0)	
C	30 (56.6)	23 (43.4)		44 (83.0)	9 (17.0)	
CNLC stage			0.788			0.518
Ib	1 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
IIa	1 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
IIb	7 (53.8)	6 (46.2)		13 (100.0)	0 (0.0)	
IIIa	11 (61.1)	7 (38.9)		16 (88.9)	2 (11.1)	

(Continued)

TABLE 2 Continued

Items, No. (%)	ORR	Non-ORR	*P*-value	DCR	Non-DCR	*P*-value
IIIb	25 (55.6)	20 (44.4)		37 (82.2)	8 (17.8)	
AFP			0.070			0.290
<400 ng/ml	31 (66.0)	16 (34.0)		43 (91.5)	4 (8.5)	
≥400 ng/ml	13 (44.8)	16 (55.2)		24 (82.8)	5 (17.2)	
UK	1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)	
Hepatectomy			0.384			1.000
No	30 (54.5)	25 (45.5)		48 (87.3)	7 (12.7)	
Yes	15 (65.2)	8 (34.8)		20 (87.0)	3 (13.0)	
Times of previous TACE			0.617			0.490
0	12 (57.1)	9 (42.9)		18 (85.7)	3 (14.3)	
1	16 (61.5)	10 (38.5)		23 (88.5)	3 (11.5)	
2	9 (64.3)	5 (35.7)		13 (92.9)	1 (7.1)	
3	4 (66.7)	2 (33.3)		6 (100.0)	0 (0.0)	
>3	4 (36.4)	7 (63.6)		8 (72.7)	3 (27.3)	
Previous treatment lines			0.577			0.538
First-line	37 (58.7)	26 (41.3)		56 (88.9)	7 (11.1)	
Second-line	7 (50.0)	7 (50.0)		11 (78.6)	3 (21.4)	
> Second-line	1 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Times of TACE, No. (%)			0.356			0.199
≤3	36 (55.4)	29 (44.6)		55 (84.6)	10 (15.4)	
>3	9 (69.2)	4 (30.8)		13 (100.0)	0 (0.0)	
Timing of camrelizumab administration, No. (%)			1.000			0.574
Before TACE	4 (66.7)	2 (33.3)		5 (83.3)	1 (16.7)	
After TACE	41 (56.9)	31 (43.1)		63 (87.5)	9 (12.5)	
Treatment cycle of camrelizumab			0.176			1.000
Q2W	0 (0.0)	2 (100.0)		2 (100.0)	0 (0.0)	
Q3W	45 (59.2)	31 (40.8)		66 (86.8)	10 (13.2)	
Cycles of camrelizumab, No. (%)			**0.023**			0.080
≤2	2 (25.0)	6 (75.0)		8 (100.0)	0 (0.0)	
3–4	11 (45.8)	13 (54.2)		18 (75.0)	6 (25.0)	
>4	32 (69.6)	14 (30.4)		42 (91.3)	4 (8.7)	
Interval between TACE and camrelizumab administration			0.454			0.658
Within 7 days	40 (59.7)	27 (40.3)		58 (86.6)	9 (13.4)	
Within 8 to 14 days	3 (60.0)	2 (40.0)		5 (100.0)	0 (0.0)	
Within 15 to 28 days	2 (33.3)	4 (66.7)		5 (83.3)	1 (16.7)	
Treatment regimen			0.341			1.000
Monotherapy of camrelizumab	21 (52.5)	19 (47.5)		35 (87.5)	5 (12.5)	
Combination therapy with TKI	24 (63.2)	14 (36.8)		33 (86.8)	5 (13.2)	

ORR, objective response rate; DCR, disease control rate; HBV, hepatitis B virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer; AFP, alpha-fetoprotein; UK, unknown; TACE, transarterial chemoembolization; Q2W, every 2 weeks; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitors. The bold values indicate the comparison with statistical significance.

risk factors related to the etiopathology of HCC, such as hepatitis B virus infection in China, is high, which results in approximately 50% of newly diagnosed HCC, as well as HCC-caused deaths, being from China, and they are characterized by more aggravating disease features at diagnosis, such as advanced stage (2–5). For instance, one epidemiological study in eastern China disclosed that the rate of hepatitis B virus infection reached 87.5% (22). In line with previous studies, we found that the rate of hepatitis B virus was 74.3% in this study. Therefore, more attention should be paid to the patients with HCC in China regarding their treatment. Thus, we enrolled 101 patients with intermediate-to-advanced HCC in China in this study. Meanwhile, we applied camrelizumab plus TACE to treat these patients and evaluated the efficacy and safety of camrelizumab plus TACE in treating patients with intermediate to advanced HCC in China.

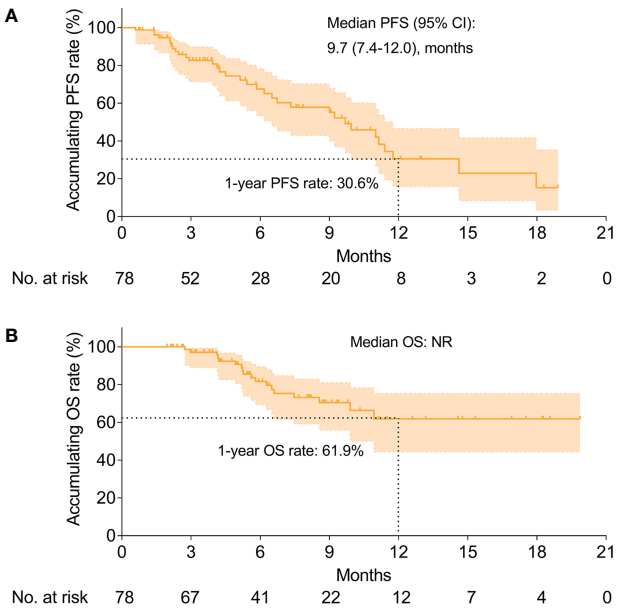

FIGURE 3
Survival profiles. The PFS **(A)** and OS **(B)** in HCC patients receiving camrelizumab plus TACE. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PFS, progression-free survival; OS, overall survival; NR, not reached.

TACE has been recognized as one of the most common treatment modalities for patients with intermediate to advanced HCC and has shown specific efficacy in those patients (23–25). For instance, one study showed that treatment with TACE in advanced HCC patients resulted in an ORR of 31.8% and a median PFS of 54 days (about 2 months) (25). Another study exhibited an ORR of 32.6% and a DCR of 82.6%, as well as a median PFS of 5.5 months after treating advanced HCC patients with TACE alone (24). In our study, the ORR was numerically higher than in previous studies (57.7% vs. 31.8%–32.6%), and the PFS was also numerically higher than previous studies (18.1 months vs. 5.5 months). The possible reason might be as follows: further TACE might lead to hypoxia, which further leads to increased PD-L1 expression, thus causing undesirable survival in HCC patients. However, the combination of PD-1 inhibitors could inhibit the linkage of PD-1 and PD-L1, which could further synergize with TACE and achieve better clinical efficacy (7–9, 19, 20).

As mentioned above, the combination of TACE with other modalities (such as TKI with or without a PD-1 inhibitor) has shown promising clinical efficacy. For instance, TACE plus sorafenib achieves a median OS of 1.55 years with a 5-year OS rate of 10.7% in HCC patients (26). TACE plus sorafenib shows an OS of 12.77 months in advanced HCC patients (27). Another retrospective study disclosed that treatment with pembrolizumab plus TACE and lenvatinib achieved an ORR of 47.1%, a DCR of 70.0%, a median PFS of 9.2 months and an OS of 18.1 months (28). In our study, the PFS was numerically higher in patients who received TACE plus TKI (9.7 months vs. 7 months), while it was similar in patients who received PD-1 inhibitor plus TACE and TKI (9.7 months vs. 9.2 months). The possible reason might be as follows: 1) TACE treatment not only causes a post-therapy neoangiogenetic reaction but also induces a low expression of Tregs *via* modulating the pro-inflammatory pathways. The combination of TACE with TKI only attenuated the neoangiogenetic reaction caused by TACE but could not affect the microenvironment. However, in our study, we combined TACE with a PD-1 inhibitor to treat HCC patients, and some patients also received TKI therapy. Therefore, in these patients, the effect of neoangiogenetic reaction and the occurrence of immune tolerance caused by TACE could be attenuated by the TKI and PD-1 inhibitor. They might achieve a better clinical outcome. Besides, the OS was numerically higher in patients who received TACE plus sorafenib compared with TACE plus TKI in our study. These phenomena might derive from the material of TACE (conventional or drug-eluting beads), the clinical features of patients, and the treatment regimen.

Beyond that, the combination of PD-1 inhibitor and TKI is also greatly interesting in the clinical field. For instance, the ORR and PFS are 46.0% and 9.3 months in unresectable hepatocellular carcinoma treated with lenvatinib plus pembrolizumab, respectively (29). Additionally, the RESCUE study disclosed an ORR of 34.3% and a PFS of 5.7 months in advanced HCC patients who received camrelizumab plus apatinib (30). Meanwhile, some cases have also been reported to respond to the combination of pembrolizumab plus sorafenib

TABLE 3 Subgroup analysis of PFS and OS.

Items	PFS			OS		
	Median PFS (95% CI), months	HR (95% CI)	*P*-value	1-year OS rate, (%)*	HR (95% CI)	*P*-value
Age			0.473			0.848
≤65 years	10.0 (7.3–12.6)	1.000		65.4	1.000	
>65 years	9.0 (4.5–13.5)	1.393 (0.563–3.445)		48.5	1.116 (0.365–3.409)	
Gender			0.832			0.856
Female	incalculable	1.000		71.4	1.000	
Male	9.7 (7.4–12.0)	0.878 (0.264–2.924)		61.0	0.873 (0.200–3.805)	
HBV			0.220			0.290
No	18.0 (incalculable)	1.000		88.9	1.000	
Yes	9.2 (5.9–12.5)	2.113 (0.639–6.992)		58.2	2.976 (0.395–22.402)	
ECOG PS score		0.926 (0.474–1.810)#	0.822		1.223 (0.501–2.984)#	0.659
0	7.3 (3.0–11.6)	–		63.8	–	
1	10.0 (7.7–12.2)	–		61.8	–	
2	incalculable	–		incalculable	–	
Child–Pugh class			0.118			0.605
A	9.0 (5.7–12.3)	1.000		56.9	1.000	
B	18.0 (6.0–30.0)	0.488 (0.199–1.199)		74.7	0.745 (0.244–2.271)	
Extrahepatic metastasis			0.509			0.143
No	11.0 (4.7–17.3)	1.000		68.8	1.000	
Yes	9.2 (5.3–13.2)	1.265 (0.630–2.537)		58.0	2.093 (0.778–5.628)	
Vascular invasion			0.170			**0.007**
No	11.0 (8.2–13.8)	1.000		76.3	1.000	
Yes	6.2 (4.4–8.0)	1.627 (0.811–3.263)		43.7	4.152 (1.476–11.680)	
BCLC stage			0.685			0.138
B	9.7 (7.0–12.4)	1.000		74.7	1.000	
C	10.0 (4.4–15.5)	1.174 (0.540–2.553)		56.7	2.563 (0.739–8.887)	
CNLC stage		1.220 (0.832–1.790)#	0.308		1.852 (0.960–3.569)#	0.066
Ib	incalculable	–		incalculable	–	
IIa	11.0 (incalculable)	–		incalculable	–	
IIb	9.7 (6.2–13.2)	–		80.0	–	
IIIa	11.8 (0.5–23.0)	–		49.8	–	
IIIb	9.2 (5.2–13.2)	–		59.6	–	
AFP			0.255			0.090
<400 ng/ml	9.0 (5.5–12.5)	1.000		71.5	1.000	
≥400 ng/ml	11.4 (8.7–14.1)	0.639 (0.295–1.383)		51.8	2.308 (0.876–6.080)	
UK	–	–		–	–	
Hepatectomy			0.631			0.587
No	9.7 (4.9–14.5)	1.000		59.5	1.000	
Yes	9.0 (2.9–15.1)	0.823 (0.371–1.826)		73.6	0.709 (0.205–2.451)	

(Continued)

TABLE 3 Continued

Items	PFS			OS		
	Median PFS (95% CI), months	HR (95% CI)	*P*-value	1-year OS rate, (%)*	HR (95% CI)	*P*-value
Times of previous TACE		0.963 (0.722–1.286)#	0.800		1.537 (1.100–2.149)#	**0.012**
0	9.7 (5.8–13.6)	–		87.8	–	
1	11.4 (5.9–16.9)	–		59.3	–	
2	9.2 (3.0–15.5)	–		67.3	–	
3	5.1 (incalculable)	–		62.5	–	
>3	9.0 (0.0–19.0)	–		24.3	–	
Previous treatment lines		0.675 (0.302–1.511)#	0.339		1.512 (0.656–3.482)#	0.332
First-line	9.7 (5.7–13.6)	–		63.9	–	
Second-line	10.0 (2.4–17.5)	–		42.1	–	
>Second-line	incalculable	–		incalculable	–	
Times of TACE, No. (%)			0.111			0.095
≤3	9.7 (5.5–13.9)	1.000		61.0	1.000	
>3	11.0 (7.7–14.3)	0.479 (0.193–1.185)		77.8	0.281 (0.063–1.245)	
Timing of camrelizumab administration, No. (%)			0.222			0.159
Before TACE	10.0 (incalculable)	1.000		60.0	1.000	
After TACE	9.2 (5.1–13.3)	3.491 (0.470–25.920)		62.4	0.345 (0.078–1.515)	
Treatment cycle of camrelizumab			0.763			0.551
Q2W	9.0 (incalculable)	1.000		incalculable	1.000	
Q3W	9.7 (5.7–13.6)	0.801 (0.189–3.389)		60.4	21.574 (0.001–517,391.446)	
Cycles of camrelizumab, No. (%)		0.503 (0.320–0.792) #	**0.003**		0.401 (0.221–0.729) #	**0.003**
≤2	6.5 (1.6–11.5)	–		60.0	–	
3–4	3.9 (2.1–5.8)	–		19.1	–	
>4	11.4 (10.5–12.3)	–		82.4	–	
Interval between TACE and camrelizumab administration		1.702 (1.039–2.790)#	**0.035**		2.542 (1.398–4.620)#	**0.002**
Within 7 days	11.0 (9.0–13.0)	–		67.5	–	
Within 8 to 14 days	6.7 (incalculable)	–		66.7	–	
Within 15 to 28 days	4.2 (3.7–4.7)	–		0.0	–	
Treatment regimen			0.824			0.460
Monotherapy of camrelizumab	10.0 (3.6–16.3)	1.000		58.6	1.000	
Combination therapy with TKI	9.7 (7.1–12.3)	1.082 (0.539–2.171)		64.0	0.704 (0.277–1.787)	

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer; AFP, alpha-fetoprotein; UK, unknown; TACE, transarterial chemoembolization; Q2W, every 2 weeks; Q3W, every 3 weeks; TKI, tyrosine kinase inhibitors.
*Median OS was incalculable, thus 1-year OS rate was used; #The variables were regarded as ordinal categorical variables instead of polytomous variable. The bold values indicate the comparison with statistical significance.

(31, 32). In our study, the ORR (57.7% vs. 34.3%–46.0%) and PFS (9.7 months vs. 5.7–9.3 months) were slightly higher compared to patients receiving PD-1 inhibitor plus TKI. This phenomenon could be explained as follows: 1) The combination of TACE, PD-1 inhibitor, and TKI might have a synergistic effect compared to the use of PD-1 inhibitor plus TKI only, thus achieving a better efficacy profile with the former one; and 2) In our study, only parts of patients received the TACE plus PD-1 inhibitor and TKI, while the remaining patients received TACE plus PD-1 inhibitor only. Therefore, the efficacy superiority of TACE plus PD-1 inhibitor and TKI in this study was small compared with PD-1 inhibitor plus TKI in other studies.

Apart from the main findings for efficacy, we also found some interesting discoveries for efficacy from the subgroup

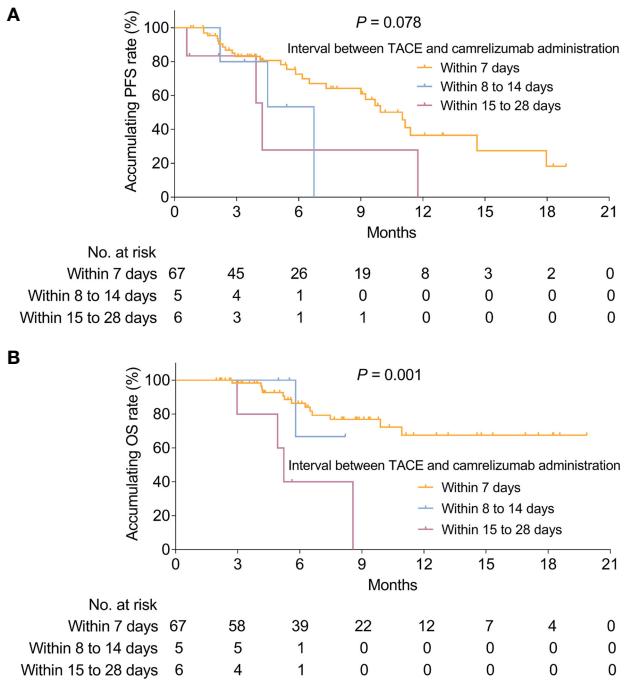

FIGURE 4
Correlation of timing between camrelizumab administration and TACE with survival. Correlation of timing between camrelizumab administration and TACE with PFS **(A)** and OS **(B)** in HCC patients receiving camrelizumab plus TACE. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PFS, progression-free survival; OS, overall survival.

analysis and multivariate Cox's regression analysis, which disclosed that the presence of vascular invasion was not associated with the ORR, DCR, or PFS, while correlated with unfavorable OS; a longer interval between camrelizumab administration and TACE was related to the unsatisfying OS; more cycles of camrelizumab were correlated with satisfactory PFS and OS; and the timing of camrelizumab administration (before and after TACE) was not associated with the PFS and OS. Possible explanations might be that: 1) Although vascular invasion in HCC patients is known to be related to pejorative survival in a wide range of studies, the occurrence of vascular invasion was not associated with the ORR, DCR, or PFS in our study, which is possible due to the relatively few HCC patients being concurrent with vascular invasion (only 42 patients) (33); 2) Previous studies have exhibited that the long-term interval between TACE and other treatment modalities might yield a worse survival compared to the short-term interval between these two treatment modalities such as radiotherapy (34). In our study, we also found that the longer interval between camrelizumab administration and TACE was related to the

TABLE 4 Factors affecting PFS and OS by multivariate Cox's proportional hazards regression analysis.

Items	PFS		OS	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
Vascular invasion (yes vs. no)	0.147	1.775 (0.818–3.852)	**0.001**	9.030 (2.355–34.629)
Higher CNLC stage	0.950	1.016 (0.619–1.667)	0.384	1.478 (0.613–3.560)
AFP (≥400 ng/ml vs. <400 ng/ml)	0.274	0.638 (0.285–1.427)	0.079	2.636 (0.895–7.762)
More times of previous TACE	0.389	0.851 (0.590–1.228)	**0.018**	1.618 (1.088–2.407)
More times of TACE	0.377	0.645 (0.243–1.708)	0.107	0.233 (0.040–1.368)
More cycles of camrelizumab	**0.002**	0.415 (0.240–0.718)	0.070	0.484 (0.220–1.062)
Longer interval between TACE and camrelizumab administration	**0.032**	1.873 (1.056–3.322)	0.097	1.811 (0.898–3.654)

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CNLC, China liver cancer; AFP, alpha-fetoprotein; TACE, transarterial chemoembolization. The bold values indicate the comparison with statistical significance.

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TABLE 5 AEs.

Items	Total	Grade 1	Grade 2	Grade 3	Grade 4
Total AEs, No. (%)	91 (90.1)	21 (20.8)	29 (28.7)	38 (37.6)	3 (3.0)
Hematologic AEs, No. (%)	91 (90.1)	24 (23.8)	27 (26.7)	37 (36.6)	3 (3.0)
Transaminase elevation, No. (%)	61 (60.4)	26 (25.7)	18 (17.8)	17 (16.8)	0 (0.0)
Thrombocytopenia, No. (%)	58 (57.4)	24 (23.8)	15 (14.9)	17 (16.8)	2 (2.0)
Hypoalbuminemia, No. (%)	55 (54.5)	35 (34.7)	19 (18.8)	1 (1.0)	0 (0.0)
Hyperbilirubinemia, No. (%)	48 (47.5)	28 (27.7)	16 (15.8)	4 (4.0)	0 (0.0)
Leukopenia, No. (%)	43 (42.6)	12 (11.9)	25 (24.8)	6 (5.9)	0 (0.0)
Neutropenia, No. (%)	41 (40.6)	17 (16.8)	12 (11.9)	11 (10.9)	1 (1.0)
Anemia, No. (%)	40 (39.6)	30 (29.7)	9 (8.9)	1 (1.0)	0 (0.0)
Albuminuria, No. (%)	27 (26.7)	17 (16.8)	8 (7.9)	2 (2.0)	0 (0.0)
Creatinine elevation, No. (%)	3 (3.0)	2 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)
Non-hematologic AEs, No. (%)	29 (28.7)	16 (15.8)	10 (9.9)	2 (2.0)	0 (0.0)
Immune-related AEs	8 (7.9)	5 (5.0)	2 (2.0)	1 (1.0)	0 (0.0)
Rash, No. (%)	7 (6.9)	6 (5.9)	1 (1.0)	0 (0.0)	0 (0.0)
RCCEP, No. (%)	6 (5.9)	3 (3.0)	3 (3.0)	0 (0.0)	0 (0.0)
Fever, No. (%)	5 (5.0)	4 (4.0)	1 (1.0)	0 (0.0)	0 (0.0)
Pain, No. (%)	5 (5.0)	4 (4.0)	1 (1.0)	0 (0.0)	0 (0.0)
Fatigue, No. (%)	5 (5.0)	3 (3.0)	1 (1.0)	1 (1.0)	0 (0.0)
Loss of appetite, No. (%)	4 (4.0)	3 (3.0)	0 (0.0)	1 (1.0)	0 (0.0)
Hand foot syndrome, No. (%)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting, No. (%)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

AEs, adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation.

unsatisfactory OS, which might be due to a decrease in intratumoral density of Tregs by TACE, further leading to an immune tolerance microenvironment. Meanwhile, the longer interval after TACE indicated the more mature the immune tolerance microenvironment, which weakened the efficacy of camrelizumab. Thus, a longer interval between camrelizumab administration and TACE caused a worse efficacy profile (20); 3) The number of cycles of camrelizumab administration was inherently determined by the clinical assessment of the responses and tolerance of patients, which implied that only the patients who responded to camrelizumab with tolerable AEs were likely to receive more cycles of camrelizumab administration. Therefore, those patients with more cycles of camrelizumab administration had a good response to camrelizumab with a tolerable and safe profile, resulting in a prolonged survival. 4) The timing of camrelizumab administration did not affect the efficacy and safety, which indicated that both strategies (camrelizumab administrated before or after TACE) were effective and safe; therefore, clinicians might choose the most suitable treatment strategy depending on the physical conditions of patients.

In terms of the safety findings, previous studies of patients with intermediate to advanced HCC treated with PD-1 inhibitor plus TACE indicated that the most common adverse events included fever, skin reactions, fatigue, vomiting, hypertension, diarrhea, thrombocytopenia, elevated AST, elevated ALT, asthenia, decreased appetite, rash, and pruritus (12, 28). Consistent with previous studies, we found that the incidence of total AEs was 90.1%. Besides, most AEs were below grade 3, including transaminase elevation, thrombocytopenia, hypoalbuminemia, hyperbilirubinemia, leukopenia, neutropenia, anemia, and albuminuria. In contrast, grade 4 AEs only occurred in three HCC patients, including grade 4 thrombocytopenia in two patients, and one patient experienced grade 4 neutropenia. These data indicated that the safety profile of treating patients with intermediate to advanced HCC with camrelizumab plus TACE was acceptable and manageable. Also, these data remind the clinicians to closely monitor the occurrence of AEs during the treatment with camrelizumab plus TACE and dispose of them in time.

Some points should be clarified in this study, such as why 7 and 14 days are set as the cut-point intervals between the TACE and camrelizumab. According to the previous study, this issue might be explained as the PD-1/PD-L1 inhibitor treatment within 24 h after TACE might achieve an elevation trend in the rabbit model (35). Thus, theoretically, the camrelizumab should be applied to HCC patients as soon as possible after the TACE treatment. However, in clinical practice, considering the liver injury, the interval between TACE and camrelizumab should be set for at least 7 days. In particular, the liver function of HCC patients would recover spontaneously within 3–7 days after TACE. Therefore, to confirm that all patients are

recovered in terms of their liver function, we set the interval as 7 days. Secondly, another cut-off time point is set as 14 days, which could be explained as that some patients might suffer from severe liver injury, which implies that they could not recover from the liver injury spontaneously, while they need extra medicine treatment for the liver injury; therefore, they need another 7 days for this treatment. In this study, the interval between TACE and camrelizumab might affect survival, implying that the shorter interval could lead to a prolonged OS profile. At the same time, more attention should be paid to the recovery of liver function in these HCC patients. Additionally, all patients receive the cTACE treatment. This is because the patients in this study mainly include those with huge and multi-focal lesions. The efficacy of DEB-TACE in these patients is unsatisfactory. Besides, the expense of DEB-TACE is also high. Therefore, no DEB-TACE was applied in this study. However, the efficacy of DEB-TACE combined with camrelizumab in HCC patients with huge and multi-focal lesions could be determined in further study.

Several limitations should not be neglected. First, this study was a single-armed study, which lacked a control group; Second, even though we found that the longer interval between camrelizumab administration and TACE was related to the unsatisfactory PFS and OS, due to the relatively small number of patients in the subgroup of timing between camrelizumab administration and TACE within 15 to 28 days and those within 8 to 14 days, this finding needed to be validated in further study; Third, 23 patients without eligible imaging assessment were excluded from the efficacy evaluation, which further reduced the number of patients available for efficacy analysis; Fourth, the short follow-up period resulted in a median OS that has not yet been reached, thus a long-term follow-up in the further studies was needed; Fifth, other outcomes (i.e., quality of life) were not analyzed in this study; Sixth, due to the prevalence of risk factors was associated with the etiopathology of HCC, such as the hepatitis B virus infection varied between HCC patients in China and other countries. Thus, geographical limitations might exist which might lead to this finding being unsuitable for HCC patients from other countries; Seventh, in this study, a large number of patients (47.5%) received the various TKI agents during the study period, which may affect the results of the present study to a certain extent.

To be conclusive, the camrelizumab plus TACE regimen is effective and safe, indicating its potential to serve as a promising treatment choice for patients with intermediate to advanced HCC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by The Institutional Review Board of Jiangsu Cancer Hospital and Jiangsu Institute of Cancer Research and The Affiliated Cancer Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RY and QX made substantial contributions to the design of the present study. Data acquisition was performed by RY, QX, QW, QZ, WZ, CC, XH, HHJ, PL, HJ, YL, YJ, YJL, LC, WW, HX, XZ, and GY. Data analysis was performed by RY, QX, QW, QZ, WZ, HX, XZ, and GY. Data interpretation was performed by RY, QX, HX, XZ, and GY. HX, XZ, and GY critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.816198/full#supplementary-material

SUPPLEMENTARY FIGURE 1
MRI images at multiple-time-points for a typical HCC patient with PR after the combination treatment. MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; PR, partial response.

SUPPLEMENTARY FIGURE 2
CT and MRI images at multiple-time-points for a typical HCC patient with PR after the combination treatment. CT, computerized tomography; MRI,

magnetic resonance imaging; HCC, hepatocellular carcinoma; PR, partial response.

SUPPLEMENTARY FIGURE 3
Comparison of the treatment response and survival between patients with and without TACE refractory. Comparison of the ORR **(A)**, PFS **(B)**, and OS **(C)** between HCC patients with and without TACE refractory. TACE, transarterial chemoembolization; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HCC, hepatocellular carcinoma.

SUPPLEMENTARY TABLE 1
Clinical characteristics between HCC patients with or without TACE refractory.

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Modified quantitative and volumetric response evaluation criteria for patients with hepatocellular carcinoma after transarterial chemoembolization

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Objective: This study aimed to investigate the cutoff value of quantitative and volumetric response evaluation criteria for patients with hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) and compare the performance of the modified criteria to one-dimensional criteria in survival prediction.

Methods: A retrospective single-center study was performed for treatment-naive patients with HCC who underwent initial TACE between June 2015 and June 2019. Treatment response assessment was performed after the first observation by contrast CT or MRI, with the measurement of diameters by modified Response Evaluation Criteria in Solid Tumors (mRECIST) and volumes by quantitative European Association for Study of the Liver (qEASL). Overall survival (OS) was the primary endpoint of this study. The new cutoff value for volumetric response evaluation criteria was created using restricted cubic splines. The performance of modified qEASL (mqEASL, with the new cutoff value) and mRECIST on survival prediction was compared by Cox regression models in internal and external validation.

Results: A total of 129 patients (mean age, 60 years ± 11 [standard deviation]; 111 men) were included and divided into training (n=90) and validation (n=39) cohorts. The cutoff value for the viable volume reduction was set at 57.0%. The mqEASL enabled separation of non-responders and responders in terms of median OS ($p<0.001$), 11.2 months (95% CI, 8.5–17.2 months) vs. 31.5 months (95% CI, 25.5–44.0 months). Two multivariate models were developed with independent prognostic factors (tumor response, metastasis, portal vein tumor thrombus, and subsequent treatment) to predict OS. Model 2 (for mqEASL) had a greater Harrel's C index, higher time-dependent area under the receiving operator characteristic curve (AUROC), and more precise calibration on 6-month survival rates than Model 1 (for mRECIST).

Conclusions: With the modified cutoff value, the quantitative and volumetric response of HCC patients to TACE becomes a precise predictor of overall survival. Further studies are needed to verify this modification before application in clinical practice.

KEYWORDS

hepatocellular carcinoma, transarterial chemoembolization, tumor response, European Association for Study of the Liver, modified response evaluation criteria in solid tumors

1 Introduction

Hepatocellular carcinoma (HCC) was the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020, with approximately 906,000 new cases and 830,000 deaths, according to statistics published by the World Health Organization (1). Most patients with HCC lost the opportunity to undergo curative treatments such as resection and liver transplantation because they had intermediate- or advanced-stage disease when diagnosed with HCC (2–4). Transarterial chemoembolization (TACE) is one of the most commonly recommended treatments for these patients according to clinical practice guidelines from various nations and regions (5–9). Furthermore, patients who showed a better response to TACE treatment in repeated sessions, as evaluated by posttreatment imaging, are likely to have more prolonged overall survival (10–12).

Among the response evaluation criteria, the modified Response Evaluation Criteria in Solid Tumors (mRECIST) is most commonly used in patients with HCC undergoing TACE (13, 14). Because chemoembolization often induces tumor necrosis rather than size shrinkage, a measurement of enhancing tumor size instead of the whole lesion has been shown to be more suitable for TACE. However, due to the nature of one-dimensional measurement, the sum of the diameters of enhancing tumors is just an approximate surrogate for the total viable tumor volume. To overcome the shortcomings of mRECIST, quantitative European Association for the Study of the Liver (qEASL) was proposed, which is a three-dimensional (3D) quantitative imaging analysis that was able to calculate viable tumor volume before and after treatment (15–17). The diagnostic accuracy of identifying tumor necrosis in HCC lesions was verified by a radiological–pathological correlation study (18). Moreover, several retrospective studies have validated the superiority of qEASL over other criteria in identifying responders and non-responders after not only TACE (19, 20) but also sorafenib (21) and Y90 radioembolization (22) in HCC patients.

However, the cutoff value for qEASL (65% of enhancing tumor volume reduction) in determining responders was derived from mRECIST (30% of maximum diameter reduction) and calculated using the formula $V=4/3\pi r^3$ (19, 20). Few studies looked into a cutoff value for tumor volume change that was close to reality. As a result, we conducted a study to modify the qEASL cutoff value so that the response evaluation of HCC patients who underwent TACE could contribute more to survival prediction.

2 Materials and methods

2.1 Patient selection and data collection

This retrospective study was approved by the Institutional Review Board, and the requirement for informed consent from patients was waived. The design of the study was in agreement with the Standards for Reporting of Diagnostic Accuracy guidelines. A list of 396 consecutive patients who underwent TACE at our institution between June 2015 and June 2019 was collected and checked for eligibility (Figure 1). The inclusion criteria were as follows: (a) age ≥18 years old, (b) HCC diagnosis (histological confirmation or clinical–radiological results of early enhancement followed by quick washout on dynamic liver imaging) in accordance with EASL or American Association for the Study of Liver Diseases guidelines (5, 7), (c) preserved liver function with Child–Pugh Class A or B, (d) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2,

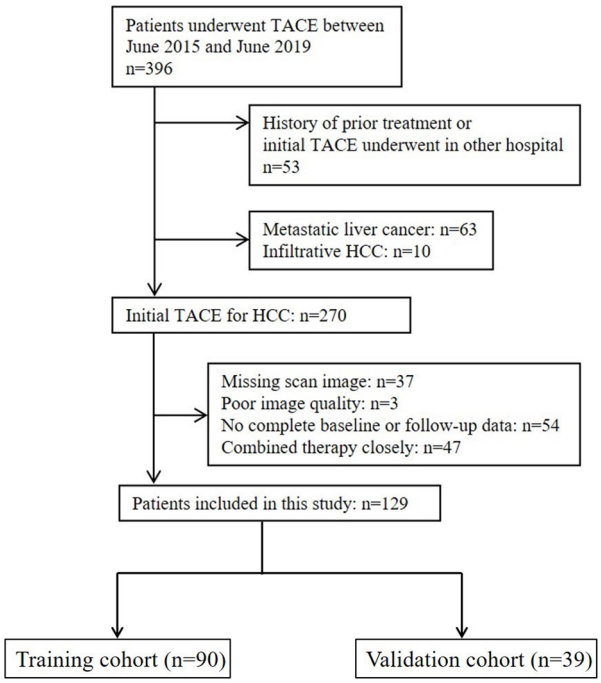

FIGURE 1
Flowchart of patients included and excluded in the study.

and (e) TACE chosen as the initial treatment. The exclusion criteria were as follows: (a) infiltrative HCC, (b) no complete pre- and posttreatment images or poor image quality with motion artifacts, (c) no baseline and/or follow-up data, and (d) a history of prior treatment other than TACE. The endpoint of this study was overall survival, and follow-up was terminated on 1 June 2021. Enrolled patients were randomly assigned to either the training or the validation cohorts at a ratio of 7:3.

2.2 Treatment

All TACE procedures were performed by three interventional radiologists (Z.L., J.S., and W.W., with TACE experience for 10, 15, and 20 years, respectively), following technical recommendations (23). Briefly, a 2.7-Fr microcatheter (Progreat, Terumo, Japan) was advanced, and the tip of the catheter was superselectively placed in the subsegmental tumor-feeding vessel (s). For conventional TACE, a water-in-oil emulsion with two volumes of lipiodol (up to 15 ml, Lipiodol Ultrafluid, Guerbet, France) and one volume of doxorubicin (50 mg/m^2 surface area) was infused, followed by embolization with 100–300 μm gelatin sponge particles (Ailicon Pharmaceutical Technology Co. Ltd., Hangzhou, China). For TACE with drug-eluting beads, a total of 80 mg of doxorubicin at a concentration of 20 mg/ml was loaded into a vial of 100–300 μm CalliSphere beads (Jiangsu Hengrui Medicine Co., Ltd., China) and mixed with 10 ml of nonionic contrast (Iodixanol, Jiangsu Hengrui Medicine Co., Ltd., China). Embolization was not stopped until the stasis of blood flow in the target artery was obtained. TACE treatment was repeated on demand every 6–8 weeks when sequential images showed evident enhancing lesions and was terminated when an objective response was not reached after consecutive sessions. A multidisciplinary liver tumor board determined subsequent treatments (including resection, radiofrequency ablation, internal radiotherapy, targeted therapy, and immunotherapy) based on changes in the patients' condition.

2.3 Image acquisition

Patients underwent either multiphasic computed tomography (CT) or magnetic resonance (MR) scans at baseline (1–2 weeks before initial TACE treatment) and follow-up. Assessment scans were performed 6–8 weeks after initial TACE. Multiphasic contrast-enhanced images on CT were obtained using multidetector CT scanners (Siemens Medical Solutions, Germany; Philips Healthcare, The Netherlands). MR imaging was performed using 3.0-Tesla MR systems (Siemens, Erlangen, Germany, parameters: TR/TE, 3.3/1.16; a 13° flip angle; matrix, 256×192; slice thickness, 2.5 mm). Multiphasic enhanced images, including arterial phase, portal venous phase, and delayed images, were obtained 20, 70, and 180 s after all intravenous contrast (iodixanol for CT and gadodiamide for MR) was administered.

2.4 Tumor response assessment

Two interventional radiologists (J.Y., with 3 years of experience, and Y.Y., with 5 years of experience) who were blinded to the patients' medical history and outcomes independently and retrospectively reviewed the scan images. Intrahepatic target tumors were identified if their longest diameter ≥1 cm, with typical intratumoral arterial enhancement, and received standardized embolization treatment. The tumor response after the first TACE was used as a prognostic factor in this study. For mRECIST, the sum of the largest diameters of target-enhancing tumors (D), avoiding major areas of internal necrosis, was measured at baseline (BL) and follow-up (UP). The percentage of diameter change was calculated as $DC = \frac{D\ (UP) - D\ (BL)}{D\ (BL)} \times\ 100[\%]$. Patients were stratified into complete response (CR, the complete disappearance of all target tumor enhancement), partial response (PR, at least a 30% decrease in the sum of the largest viable tumor diameters), progressive disease (PD, at least a 20% increase in the sum of the largest viable tumor diameters, or new intrahepatic lesions), and stable disease (SD, neither PR nor PD). Responders included patients with CR and PR, while patients with SD and PD were divided into non-responders.

Quantitative EASL was performed using 3D Slicer software (https://www.slicer.org), a free-to-use platform for quantitative imaging analysis (24), following the principles described previously (15–17). Briefly, semiautomatic 3D tumor segmentation (Seg1) was performed on arterial phase enhanced images. After subtracting unenhanced images from enhanced images to remove background value, the enhancement value of liver parenchyma (as the threshold) was calculated by averaging values of three points of surrounding healthy tissues selected by experienced radiologists. A threshold tool was used to automatically segment voxels within Seg1 where the enhancement values were greater than the threshold. The volume of new segmentation (Seg2) was calculated to represent the viable tumor volume (VTV). Volume-based qEASL was adopted in this study (Figure 2). Both VTV at baseline (BL) and follow-up (UP) were collected to calculate the percentage of viable tumor volume change (VC): $VC = \frac{VTV\ (UP) - VTV\ (BL)}{VTV\ (BL)} \times\ 100\ [\%]$. Patients were divided into responders and non-responders with a cutoff value created in restricted cubic spline analysis as described below. Patients with new lesions were identified as non-responders (with progressive disease) and were excluded from the exploration of the cutoff value. Briefly, when a reduction in viable tumor volume reached or was greater than the cutoff value, the patient was classified as responder in mqEASL. On the contrary, when the criteria of responder was not reached or new lesions occurred, the patient was classified as non-responder in mqEASL.

2.5 Statistical analysis

Continuous variables are presented as the means with standard deviations or medians with interquartile ranges (IQRs) and were compared by Student's t-test or the Mann–Whitney U-test. Categorical variables were summarized as numbers with percentages and compared by Fisher's exact test. Correlations between response evaluation indexes were presented in scatter plots and fitted using a linear regression model. The association between volume change and hazard ratio of death was flexibly modeled by using four-knot restricted cubic splines. The volume change value whose corresponding hazard ratio of death equaled 1 was selected as the cutoff value to stratify responders and non-responders in modified qEASL (mqEASL). The evaluation agreement between mRECIST and mqEASL was assessed by

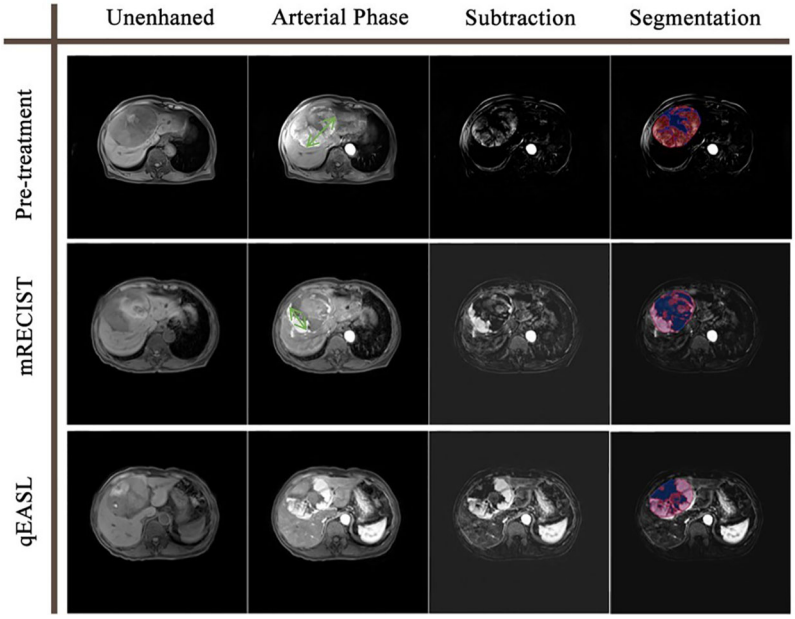

FIGURE 2
Tumor response evaluation based on the contrast-enhanced MR of a 78-year-old man with one HCC tumor. The green double-sided arrows represent the measurement of the diameter of the largest viable tumor on arterial phase images. The color maps represent the segmentation using the qEASL method, where blue maps illustrate inactive areas and red maps indicate viable tumors. The viable tumor volume was 494.2 cm^3 at baseline and 292.5 cm^3 after the initial TACE. The 40.8% viable tumor volume reduction suggested that this patient was a non-responder to TACE. In comparison, the diameter of the viable tumor was 11.5 cm at baseline and 6.7 cm after the initial TACE. The 41.7% diameter reduction suggested that this patient was a responder to TACE. The disagreement of the two evaluation methods may result from the irregular shape of the necrosis zone.

the McNemar test, and the kappa statistic was calculated. Poor, moderate, and excellent agreement was judged by kappa values of <0.4, 0.4–0.75, and >0.75, respectively (25).

Overall survival (OS) was calculated from the day of the first TACE session to the date of death from any cause. Patients were censored at the last follow-up time point or the end of the observation period if they were lost to follow-up or still alive. Survival curves were estimated with the Kaplan–Meier method and compared with the log-rank test. The Cox proportional hazards model was used to identify predictors that have a significant influence on the survival of patients in both univariate and multivariate analyses. To compare the predictive performance of mRECIST and mqEASL in terms of overall survival, two Cox regression models were built based on the training cohort with pretreatment predictors together with posttreatment response markers evaluated by either mRECIST (Model 1) or mqEASL (Model 2). The discrimination and calibration of the two models were measured and compared in both the training and validation cohorts using Harrel's C index, area under the time-dependent receiving operator characteristic curve (AUROC), and calibration curves. All statistical tests were conducted at the two-sided 5% significance level using R version 4.1.0.

3 Results

3.1 Patient characteristics

A group of 129 patients were included and divided into training (n=90) and validation (n=39) cohorts (Figure 1). The characteristics of the patients are summarized and compared in Table 1. The majority of HCC patients were male (training: n=79 [87.8%], validation: n=32 [82.1%]). Most patients tested positive for hepatitis virus B infection (training: n=75 [83.3%], validation: n=26 [66.7%]). Over two-thirds of the patients had stage A or B disease, according to the Barcelona Clinic for Liver Cancer (BCLC) system (training: n=63 [70.0%], validation: n=27 [69.2%]). Characteristics except etiology (p=0.044) were comparable between the two cohorts.

3.2 Cutoff value of viable tumor volume change

The expected volume change (EVC) was calculated by the following formula: EVC=[(1+Diameter change)^3−1]×100(%). The relationships between EVC and VC are depicted in the scatter plot (Figure 3A). The fitted linear regression equation for EVC and VC was VC=1.88×EVC+69.75 (far from the ideal: VC=EVC). Simply using the expected volume change as a substitute for the actual viable volume change would cause imprecision. The relationship between viable tumor volume change and risk of mortality in the training and validation cohorts is shown in Figures 3B, C. A decrease in viable volume of more than 57.0% was revealed to be a protective factor against mortality. On the other hand, a decrease in viable volume that did not reach 57.0% or an increase in viable volume suggested a quick increase in the risk of death. Consequently, a decrease of 57.0% was selected as the cutoff value in mqEASL (responder, ≥57.0% decrease; non-responder, responder criteria not met or new lesion). The evaluation agreement of mRECIST and mqEASL in all enrolled

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TABLE 1 Baseline patient characteristics.

Patient Characteristic	Training	Validation	p-value
(N=129)	n=90	n=39	
Sex			0.414
Male/female	79/11 (87.8%/12.2%)	32/7 (82.1%/17.9%)	
Age (year, mean ± SD)	59 ± 11	63 ± 10	0.079
Etiology			0.044
None/HBV/other	8/75/7 (8.9%/83.3%/7.8%)	10/26/3 (25.6%/66.7%/7.7%)	
ECOG PS			0.658
0/1/2	73/15/2 (81.1%/16.7%/2.2%)	30/7/2 (76.9%/17.9%/5.1%)	
Child–Pugh			1.000
A/B	81/9 (90.0%/10.0%)	36/3 (92.3%/7.7%)	
ALBI			1.000
1/2/3	36/51/3 (40.0%/56.7%/3.3%)	16/22/1 (41.0%/56.4%/2.6%)	
Tumor number (median, IQR)	2 (1~3)	2 (1~3)	0.502
Diameter of largest tumor			1.000
<5 cm/≥5 cm	49/41 (54.4%/45.6%)	21/18 (53.8%/46.2%)	
Up-to-seven			0.702
In/Beyond	49/41 (54.4%/45.6%)	23/16 (59%/41%)	
AFP			0.563
<200 ng/ml/≥200 ng/ml	54/36 (60.0%/40.0%)	21/18 (53.8%/46.2%)	
Metastasis			0.635
Negative/positive	73/17 (81.1%/18.9%)	30/9 (76.9%/23.1%)	
PVTT			1.000
Negative/positive	74/16 (82.2%/17.8%)	32/7 (82.1%/17.9%)	
BCLC stage			0.233
A/B/C	25/38/27 (27.8%/42.2%/30.0%)	16/11/12 (41.0%/28.2%/30.8%)	
TACE type			0.806
Conventional/DEB	74/16 (82.2%/17.8%)	31/8 (79.5%/20.5%)	
TACE sessions(median, IQR)	3 (2~4)	3 (2~4)	0.733
Image interval (months, median, IQR)	2 (1.5~2.5)	2 (1.5~2.5)	0.633
mRECIST			0.548
Complete response	14 (15.6%)	9 (23.1%)	
Partial response	34 (37.8%)	11 (28.2%)	
Stable disease	27 (30.0%)	14 (35.9%)	
Progressive disease	15 (16.7%)	5 (12.8%)	
Subsequent treatment			0.194
None	47 (52.2%)	20 (51.3%)	
Locoregional	30 (33.3%)	8 (20.5%)	
Systemic	7 (7.8%)	5 (12.8%)	
Combined	6 (6.7%)	6 (15.4%)	

Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. HBV, hepatitis B virus infection; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ALBI, albumin–bilirubin scores; IQR, interquartile range; AFP, alpha fetoprotein; PVTT, portal vein tumor thrombi; BCLC, Barcelona Clinic Liver Cancer; DEB, drug eluting beads; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

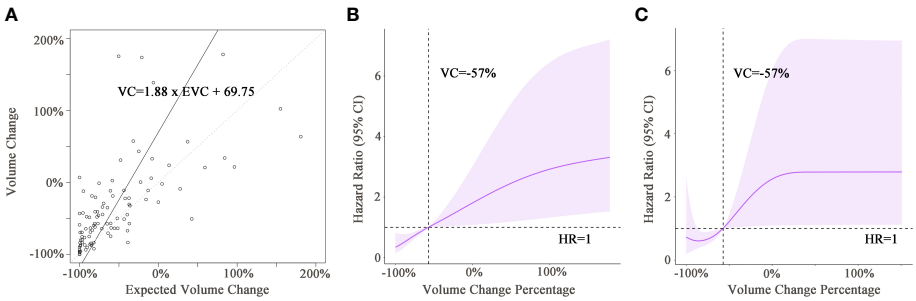

FIGURE 3
(A) The scatter plot shows the correlation between the expected viable volume change and actual viable volume change. The full line was fitted by linear regression models, with the equation presented in the rectangular frame. The dotted line is the line of reference for VC = EVC. **(B, C)** Graphs of restricted cubic spline with 95% confidence intervals for volume change and hazard ratio of death in the training cohort **(B)** and validation cohort **(C)**. Black dotted lines indicate that the hazard ratio of death equaled 1 when the volume change was −57% in both cohorts. VC, viable tumor volume change; EVC, expected viable tumor volume change; HR, hazard ratio.

patients is summarized in Supplementary Table S1. The kappa value was 0.5977 (95% CI, 0.4596–0.7359), indicating only moderate agreement (McNemar test p=0.327).

3.3 Survival analysis

During the observation period, 106 patients died (training: n=74, validation: n=32), and 23 patients were censored due to the termination of the observation period (training: n=16, validation: n=7). The median OS of the entire group was 22.4 months (95% CI, 17.0–26.6 months). Notably, in the training cohort (Figures 4A, B), the mqEASL enabled stronger separation of non-responders and responders in terms of median OS, 11.2 months (95% CI, 8.5–17.2 months) vs. 31.5 months (95% CI, 25.5–44.0 months) for mRECIST (p<0.001) and 10.1 months (95% CI, 7.9–17.0 months) vs. 39.8 months (95% CI, 27.9–48.3 months) for mqEASL (p<0.001). In the validation cohort (Figures 4C, D), the difference in overall survival between non-responders and responders in mRECIST was not significant, 13.6 months (95% CI, 11.4–30.2 months) vs. 25.0 months (95% CI, 18.3–49.7 months) for mRECIST (p=0.072), and 12.5 months (95% CI, 9.7–30.2 months) vs. 30.9 months (95% CI, 23.3–NA months) for mqEASL (p=0.004).

3.4 Univariate and multivariate analyses

The results of univariate and multivariate analyses in the training cohort are summarized in Supplementary Table S2. Independent prognostic factors (not considering response markers) were identified as follows: presence of metastasis (p<0.001), presence of portal vein tumor thrombus (p=0.002), and subsequent treatment (p=0.034).

3.5 Comparison of mRECIST and mqEASL in survival prediction

To compare the survival prediction performance of mRECIST and mqEASL in a multivariate setting, two Cox regression models (Supplementary Table S3) were created as follows:

Model 1: linear predictor (LP) =1.68×Metastasis + 1.43×PVTT − 0.47×Subsequent treatment − 1.08×Responder 1

Model 2: LP=1.88×Metastasis + 0.92×PVTT − 0.36×Subsequent treatment − 1.41×Responder 2

"Metastasis," "PVTT," and "responder" are binary variables that have a value of 0 for no metastasis, no PVTT, and non-responder and a value of 1 for metastasis, PVTT, and responder. "Subsequent treatment" is an ordinal categorical variable with a value of 0 for none, 1 for locoregional therapy, 2 for systemic therapy, and 3 for combined therapy.

The coefficient of Responder 2 (based on mqEASL) was greater than that of Responder 1 (based on mRECIST). The Harrel's C index of Model 2 was higher than that of Model 1 in both the training and validation cohorts (training [1 vs 2]: 0.778 ± 0.026 vs. 0.795 ± 0.024, validation [1 vs 2]: 0.725 ± 0.043 vs. 0.759 ± 0.041). The 6-month, 1-year, and 2-year AUROC values of Model 2 were also higher than those of Model 1 in both the training (Figure 5A) and validation (Figure 5B) cohorts, suggesting favorable discrimination of mqEASL over mRECIST. The calibration curves of the two models are shown in Figure 6. Model 2 showed better consistency between the predicted probability of 6-month and 1-year OS and the actual outcomes in the training cohort (Figure 6A). The consistency of Model 2 in 6-month OS was further confirmed by external validation (Figure 6B).

4 Discussion

Our study proposed a valid cutoff value for quantitative and volumetric tumor response evaluation criteria. The modified qEASL criteria are competent for identifying non-responders to TACE and predicting overall survival.

To date, a variety of therapies have been available for patients with HCC at different disease stages. The prompt transition from ineffective therapy to other attempts is essential for patients' overall survival. Transarterial chemoembolization is one of the most effective and widely used locoregional therapies. Several scoring systems were developed to identify patients who were unlikely to benefit from repeated TACE, such as the ART (Assessment for Retreatment with TACE) score and ABCR (Alpha fetal Protein, BCLC, Child–Pugh, Response) score (26–28). Within these scores, the radiological tumor

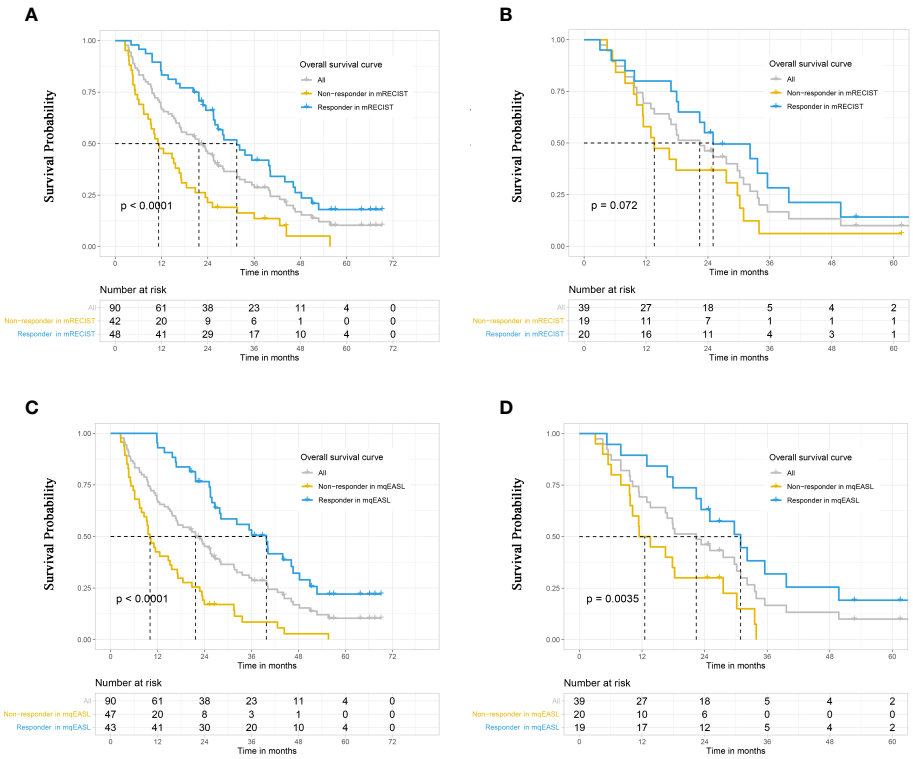

FIGURE 4
Kaplan–Meier curves to compare survival between different groups in the training cohort **(A, B)** and validation cohort **(C, D)**. Responders and non-responders were stratified after initial TACE according to tumor response, which was evaluated by the methods of mRECIST **(A, C)** and mqEASL **(B, D)**. The result of the log-rank test (p-value) is marked on each graph. mRECIST, modified Response Evaluation Criteria in Solid Tumors; mqEASL, modified quantitative European Association for Study of the Liver.

response is a significant factor (29). When non-responders to TACE are identified early, systemic or combined therapies can be used before liver function deteriorates (30–33).

Currently used criteria for tumor response evaluation, including mRECIST and EASL, adopt 1- or 2-dimensional measurements to reflect tumor extent. In recent years, the newly developed qEASL criteria have demonstrated superiority in quantifying enhancing tumor volume (17, 18, 20–22). The example in Figure 2 shows a familiar situation in clinical practice. The irregular shape of the internal necrosis area hindered the measurement of viable tumor diameter after TACE treatment, which could be overcome by a 3D measurement of viable tumor volume. In the ideal scenario, where tumor lesions are regular spheres and shrink symmetrically, a ≥30% decrease in diameter or a ≥50% decrease in section area approximately equaled a ≥65% decrease in volume. However, the actuality fell far short of the ideal. All of the former studies investigating qEASL adopted the calculated cutoff value (65% decrease in tumor volume) in dividing non-responders and

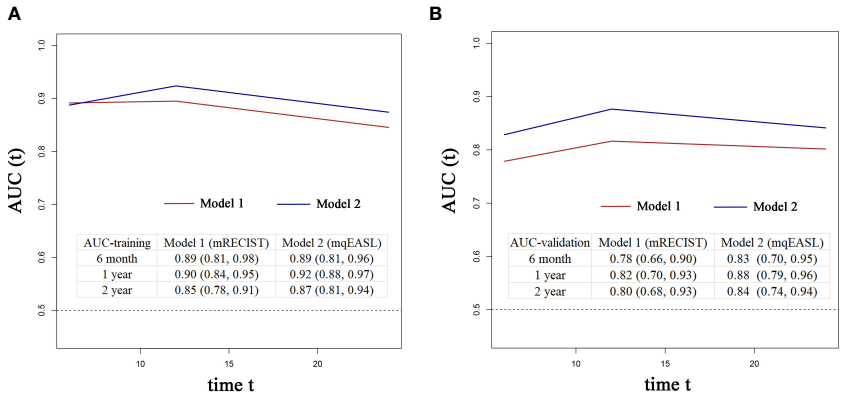

FIGURE 5
Time-dependent AUROC values of Model 1 and Model 2 in the training cohort **(A)** and validation cohort **(B)**. The inserted tables show the AUROC values with 95% confidence intervals of the models at different time points. AUC, area under the curve.

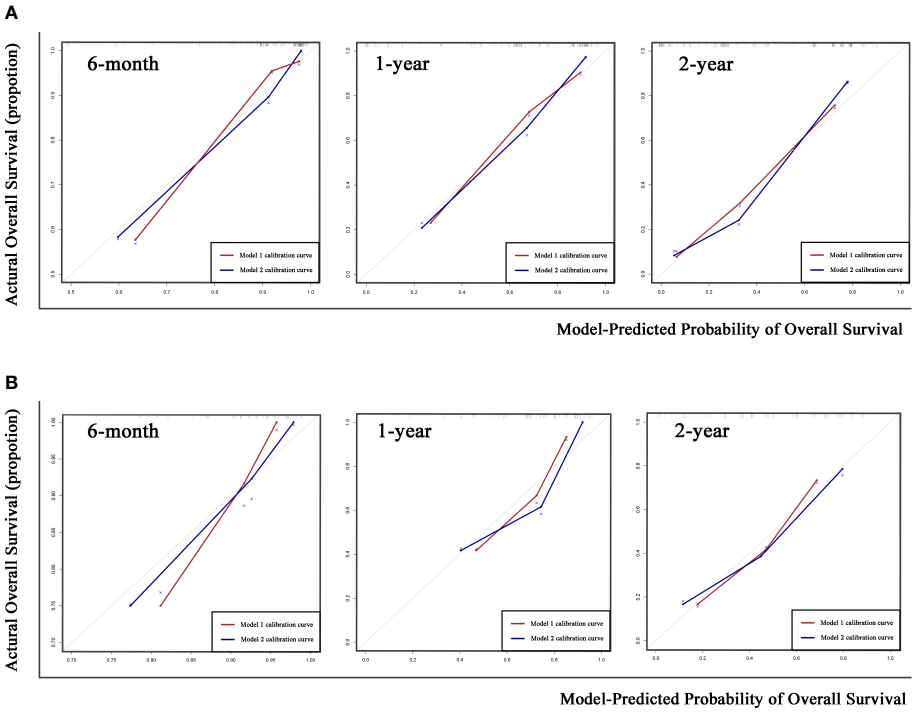

FIGURE 6
Calibration curves of the two prediction models for 6-month, 1-year, and 2-year overall survival (OS) in the training cohort **(A)** and validation cohort **(B)**. Gray dotted lines represent the calibration curve of the most ideal predictive method.

responders after different treatments. Our study investigated the relationship between expected volume change and actual volume change (VC=1.88×EVC+69.75). The findings revealed that the calculated volume change of inhomogeneous liver tumors based on diameter change does not match reality. As a result, the calculated cutoff value for qEASL would cause response evaluation inaccuracy.

A new cutoff value for volumetric response evaluation (≥57.0% decrease in enhancing tumor volume for responders) was proposed in this study, with the aim that stratification of responders and non-responders could be more capable of predicting survival. The previously used cutoff value (65% decrease, qEASL) was stricter than the modified cutoff value (57.0% decrease, mqEASL). Under the stricter rules, some patients who could benefit from TACE would be classified as non-responders. It may cause increased sensitivity but decreased specificity. Furthermore, there was only moderate agreement between mRECIST and mqEASL (kappa value=0.5977), emphasizing the necessity of comparing the two criteria.

The performance of the mqEASL was confirmed in a multivariate way by both internal and external validations. The prediction model created with independent prognostic factors (metastasis, PVTT, and subsequent treatment) and the mqEASL response marker demonstrated superior discrimination and calibration than that with the mRECIST response marker. There was no significant difference in the calibration of the two models with regard to predicting the 2-year survival rate. This could be explained by the fact that the tumor response to the initial TACE was related to a better prognosis in the short term (6 months and 1 year). In contrast, the long-term survival outcomes were influenced by a variety of factors (34, 35). Different treatment modalities strongly affected the long-term survival. When HCC advanced into a systemic disease, systemic and combined therapies as recommended can actually prolonged patients` overall survival. One doubt about the mqEASL is that the postprocessing steps take a lot of time. In our experience, once the segment of whole tumor lesion(s) and the threshold were confirmed, the volume of viable tumor was automatically calculated by the software. It takes approximately 5–20 min for each patient. The accurate evaluation of tumor burden instead of using diameter for substitution requires more time. The development of artificial intelligence will make mqEASL easier to perform in clinical practice.

There are some limitations to our study. First, the nature of retrospective studies introduced unavoidable biases. Second, the sample size was barely enough. The total number of deaths (74/90) limited the number of candidate variables that could be used in the multivariate Cox regression analysis to seven, with a ratio of 10 events per variable. Moreover, a larger external validation cohort will be required before mqEASL can be applied in clinical practice. Third, since CT and MRI were parallelly adopted in clinical practice, we included both image types for evaluation. Previous studies have proven that the qEASL criteria can be applied to multiphasic CT or MRI (19, 20). However, a small portion of patients in our study received different types of scans at baseline and follow-up. Whether volumetric evaluation criteria could be applied in this situation needs more investigation. Lastly, two different type of TACE methods were applied to patients with HCC, which may increase the heterogeneity of this study. In further analysis, the proportion of responders between conventional and DEB TACE groups showed no significance (Supplementary Table S4). In the univariate analysis of prognostic factors for survival, TACE type failed to stand out

(Supplementary Table S2). Thus, we supposed that the different TACE methods had little influence on tumor response and overall survival.

In conclusion, the modified volumetric and quantitative response evaluation criteria could enable more accurate identification of non-responders among HCC patients to TACE treatment. The new response marker was more competent to predict overall survival than mRECIST.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Guarantor of integrity of entire study, CN. Study concepts/study design or data acquisition or data analysis/interpretation, all authors. Manuscript drafting or manuscript revision for important intellectual content, all authors. All authors agrees to ensure any questions related to the work are appropriately resolved. Literature research, JX, YY, JY, and LC. Clinical studies, YY, JY, ZL, JS, WW, and CN. Statistical analysis, JX, LC, and CN. Manuscript editing, JX, YY, JY, LC, and CN.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.957722/full#supplementary-material

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Adjuvant effect of herbal medicine on transarterial chemoembolization in patients with hepatocellular carcinoma: A systematic review and meta-analysis

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Objectives: Primary hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths, especially in Asian countries. As a practical treatment option, transarterial chemoembolization (TACE) has been well applied; however, its limited efficacy remains challenging. This study analyzed the adjuvant effects of herbal medicine on TACE to determine whether it improves clinical outcomes in patients with HCC.

Methods: A systematic review and meta-analysis was performed to compare the adjuvant effects of herbal medicine on TACE versus TACE therapy alone. We searched the literature from eight databases since January 2011.

Results: Twenty-five studies involving 2,623 participants were selected. The adjuvant therapy of herbal medicine on TACE improved the overall survival at 0.5 years (OR = 1.70; 95% CI 1.21-2.38), 1 year (OR = 2.01; 95% CI 1.65-2.46), 2 years (OR = 1.83; 95% CI 1.20-2.80), and 3 years (OR = 1.90; 95% CI 1.25-2.91). The combination therapy also increased the tumor response rate (OR = 1.84; 95% CI 1.40-2.42).

Conclusions: Despite the unsatisfactory quality of the included studies, the adjuvant therapy of herbal medicine on TACE may provide survival benefits to patients with HCC.

Systematic reviews registration: http://www.crd.york.ac.uk/PROSPERO, identifier (376691).

KEYWORDS

herbal medicine (HM), transarterial chemoembolization, hepatocellular carcinoma, overall survival (OS), systematic review & meta-analysis

1 Introduction

Hepatocellular carcinoma (HCC) is the leading cause of cancer-related deaths, with an incidence of 9.3 and a mortality rate of 8.5 per 100,000 in 2018 worldwide (1). Since most HCCs are asymptomatic until they reach an advanced or late stage, HCC is difficult to diagnose and has a very poor prognosis (2). The mortality of patients with HCC has remained unchanged over the past decade (3, 4).

Adequate treatments for HCC, including surgical resection, chemotherapy, radiation therapy, radiofrequency ablation, and transarterial chemoembolization (TACE), have improved the 5-year survival rate of HCC from 9% to 18% between 2001 and 2019 (4–7). Among those therapeutics, TACE is the first-line treatment for patients with early-stage and localized HCC and causes tumor necrosis by injection of chemotherapeutic agents into the hepatic artery (8). TACE is not only applied in the early stage but is also frequently used in the unresectable and late stages for palliative care in HCC patients (9).

Approximately 80% of patients with HCC have liver fibrosis, resulting in liver cirrhosis due to chronic inflammation in the liver (10). Although TACE is a topical treatment that can minimize systemic inflammation, TACE accelerates the hepato-fibrotic changes because of its inevitable cytotoxic effects (11). Patients who receive TACE therapy sometimes suffer from complications such as acute cholecystitis, leukopenia, pulmonary embolism, hepatic abscess, bile duct injury, and gastric mucosa injury (12–14). The limitations of TACE in the clinic include not only an insufficient response but also the adverse effects listed above (15).

On the other hand, herbal medicine has been prescribed as an option for patients with hepatic inflammation and liver fibrosis in Asian countries (16, 17). In 1996, the effect of combination therapy of TACE and herbal drugs was first reported (18), and a systematic review of the beneficial outcomes of herbal medicine on TACE was published in 2013 (19). To date, the adjuvant therapy of herbal drugs on TACE for patients with HCC has been further practiced and has been continued; however, no comprehensive evaluation of the combination therapy has been conducted in the last 10 years.

Herein, we conducted a systematic review and meta-analysis to evaluate the adjuvant effect of herbal medicine on TACE in patients with HCC.

2 Materials and methods

2.1 Protocol and registration

This systematic review, including a meta-analysis, was conducted based on the PRISMA guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (ID: 376691, http://www.crd.york.ac.uk/PROSPERO).

2.2 Search strategy

Eight databases, including the PubMed, Cochrane, ClinicalTrials.gov, EMBASE, Google Scholar, Chinese National Knowledge Infrastructure, Research Information Sharing Service, and Korean Studies Information Service System databases, were searched after January 2011 using keywords related to primary HCC, herbal medicine, TACE and overall survival. The search terms were (hepatocellular carcinoma OR hepatocellular neoplasms OR liver cancer OR liver neoplasms OR primary hepatic cancer OR intrahepatic neoplasms OR liver adenoma OR liver carcinoma OR hepatocellular adenoma OR HCC) AND (TACE OR transcatheter arterial chemoembolization OR embolization) AND (herb OR herbal medicine OR herbal decoction OR herbal drugs OR phytotherapy OR Korean medicine OR Chinese medicine).

2.3 Selection criteria

The studies that met the following criteria were included: clinical studies comparing the effects between 'TACE combined with herbal drugs' and 'TACE-only' in patients with primary HCC. There was no limit on the language, and studies that did not meet the above criteria were excluded.

2.4 Data extraction and review process

After screening the title and abstract of all the studies, the full text of the relevant articles was assessed by two reviewers. Any disagreement was resolved by discussion or consensus with the corresponding author. We conducted a systematic review on the clinical benefits of herbal medicine combined with TACE compared to TACE alone. We extracted the following data: name of the first author, patient information, sample size, herbal medicine, duration of herbal medicine, observation period, and outcome measurements (overall survival at 0.5, 1, 2, and 3 years, number of complete/partial responses, and/or Karnofsky performance status (KPS) score) of the study.

A meta-analysis was performed using odds ratios (ORs) for the overall survival rate and tumor response rate and weighted mean differences (WMDs) for the KPS score with 95% confidence intervals (CIs). Random-effect models were used due to heterogeneity. Dichotomous data are expressed as the OR with 95% CI. WMDs with the 95% CI were calculated for continuous data. The Higgins I^2 test was used to assess the heterogeneity of the data (20). Statistical significance was set at $P < 0.05$. Review Manager 5.4.1 was used for the analysis (http://www.tech.cochrane.org/revman) (accessed on 15 July 2022) (21).

3 Results

3.1 Characteristics of the included studies

A total of 570 relevant articles were initially searched, and 25 studies were finally selected for this study (Figure 1). The total number of participants was 2,623 (male 1957, female 666), with 1,322 who took the combination therapy and 1,301 who only had TACE. The information for stage was obtained from 655 subjects, and

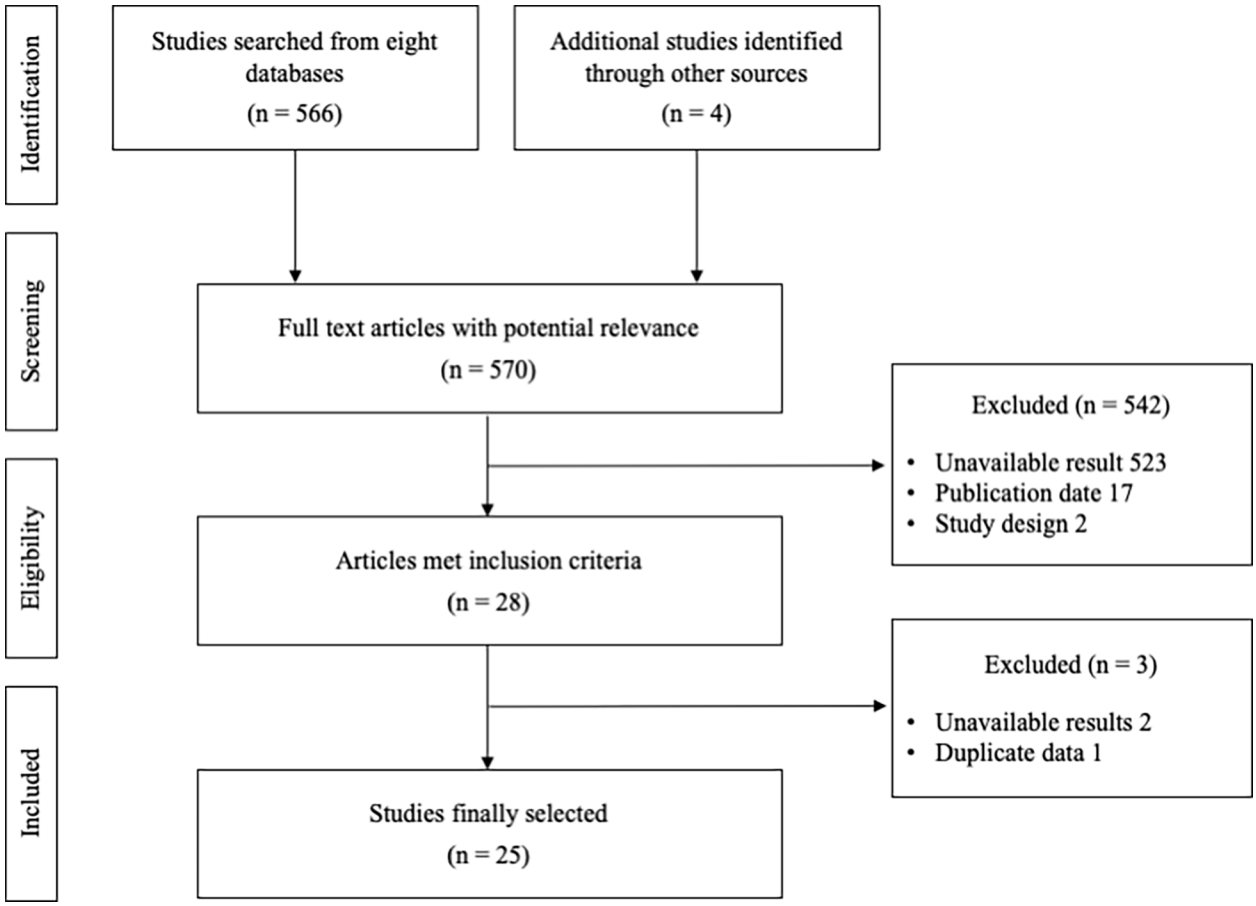

FIGURE 1
Flow diagram of study selection process.

the Child–Pugh scores were determined from 1,746 patients (Table 1). There was no significant difference in baseline characteristics between the intervention (TACE+HM) and control (TACE-only), regarding age, sex, HCC stage, Child-Pugh grade, etc. respectively (Table 1).

Twenty-three kinds of herbal medicines were administered for an average of 14.0 ± 12.2 weeks. The mean observation period was 1.84 years, and overall survival was evaluated as the primary measurement at four main time points (0.5, 1, 2, and/or 3 years), along with the tumor response rate and quality of life as secondary measurements (Table 1).

3.2 Herbal medicine used for combined therapy with TACE

The kinds of herbal medicine and their composition were all provided, as summarized in Supplementary Table 1. Yipi Yanggan decoction was applied in three patients, and the rest of the patients had all different kinds (Table 2). The most frequently used herbs were *Atractylodes macrocephala* Koidz. (17 times), Wolfiporia extensa (15 times), *Curcuma longa* L. (12 times), *Bupleurum falcatum* L. (12 times), *Astragalus propinquus* Schischk (11 times) (Supplementary Table 2).

3.3 Benefits in overall survival (primary measurement)

From the meta-analysis of the overall survival rate, the combination therapy showed a significant improvement in the survival rate at all measured points (Figure 2); OR = 1.70 at 0.5 years (95% CI 1.21-2.38; P < 0.002, 15 studies, 1,131 participants) (Figure 3), OR = 2.01 at 1 year (95% CI 1.65-2.46; P < 0.00001, 25 studies, 2,623 participants) (Figure 4), OR = 1.83 at 2 years (95% CI 1.20-2.80; P = 0.005, 10 studies, 1,062 participants) (Figure 5), and OR = 1.90 at 3 years (95% CI 1.25-2.91; P = 0.003, 8 studies, 1,126 participants) (Figure 6).

3.4 Benefits in tumor response rate and quality of life (secondary measurement)

As secondary measurements, the meta-analysis for the response rate of treatment was significantly increased in the combination group as the OR = 1.84 (95% CI 1.40-2.42; P < 0.0001) from 13 studies (n=1,159) (Figure 7).

Quality of life measured by the KPS score was significantly improved by combination therapy, with an WMD = 10.62 (95% CI 7.11–14.13; P < 0.00001) from 5 studies (n = 411) (Figure 8).

TABLE 1 Basic characteristics of the included studies.

Variable	Intervention (TACE+HM)	Control (TACE-only)	Total
N. of studies			25
N. of participants (%)			
Male	*981	976	1,957 (74.6)
Female	341	325	666 (25.4)
Total	1,322	1,301	2,623 (100.0)
Mean age of participants*	53.5 ± 6.7	53.4 ± 5.7	53.4 ± 6.4
HCC stage (N. of participants, %)			
2	136	129	265 (10.1)
3	168	173	341 (13.0)
4	24	25	49 (1.9)
Unknown	994	974	1,968 (75.0)
Child-Pugh score (N. of participants, %)			
A	621	621	1,242 (47.4)
B	241	237	478 (18.2)
C	11	15	26 (1.0)
Unknown	449	428	877 (33.4)
Kinds of herbal medicine			23
Mean treatment period (weeks)			14.0 ± 12.2
Mean observation period (years)			1.84
Outcome measurement (N. of studies)			
Overall survival			25
Tumor response rate			13
Performance status (KPS)			5
Publication year (N. of studies, %)			
2011-2015			12
2016-2021			13
Country (N. of studies, %)			
China			23
USA			2

TACE; transarterial chemoembolization, HM; herbal medicine, HCC; hepatocellular carcinoma, CR; complete response, PR; partial response, KPS; Karnofsky performance score, AFP; α-fetoprotein.
* The mean age was estimated using the presented mean age of each study (from 24 studies).

4 Discussion

The well-known risk factors for HCC are infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), excessive alcohol consumption, and nonalcoholic fatty liver disease (NAFLD) (47–49). In Asian countries, including China, 70~80% of HCC cases are known to be caused by HBV infections (50), while most of our data for meta-analysis did not describe the causes of HCC. As it is known, there is a male-predominance of HCC patients, and our data showed a 3.0-fold higher number of male patients than female patients (Table 1).

From 25 studies containing 2,623 participants (1,322 herbal interventions), we found a 1.29-fold survival benefit compared to the TACE-only group (primary endpoint) (Figure 2). The present results may indicate that the add-on therapy on TACE obtained a positive clinical outcome on survival gain. In fact, TACE therapy is usually coadapted with chemotherapies (51). A study reported a 1.6-fold improvement in the survival rate in patients with HCC with Child–Pugh score A using an adjuvant therapy of sorafenib with TACE (52), and that study's data was slightly superior to our data. In our study, the majority of the participants for whom the stage information was provided (only 25% of the total participants) were stages II and III, and the majority of the patients (from 50% of

TABLE 2 Detailed information of included studies.

First author (year)	N. of participants (M/F) HM+T:T-only	TACE type (chemotherapeutic drugs)	Herbal medicine (Chinese)	Duration of herbal medicine	Outcome measurements
Li et al. (2011) (22)	74 (60/14) 38:36	cTACE (5-FU, DDP, THP)	Herbal decoction*	8 weeks	Overall survival at 0.5-, 1-year Number of CR, PR
Lu Y. (2011) (23)	66 (52/14) 33:33	cTACE (5-FU, EPI, L-OHP)	Jianpi Jiedu decoction (健脾解毒汤)	12 weeks	Overall survival at 0.5-, 1-year Quality of life (KPS)
Tian et al. (2012) (24)	133 (77/56) 70:63	cTACE (5-FU, ADM, DDP, MMC)	Jinapi Xiaoji decoction (健脾小蓟汤)	8-12 weeks	Overall survival at 1-, 2-, 3-year Number of CR, PR
Zhang et al. (2012) (25)	83 (54/29) 43:40	cTACE (5-FU, DDP, MMC, THP)	Herbal decoction*	8 weeks	Overall survival at 1-year Number of CR, PR
Zhou et al. (2012) (26)	59 (36/23) 32:27	cTACE (DDP, GEM)	Herbal decoction*	4 weeks	Overall survival at 0.5-, 1-, 2-year Number of CR, PR
Han et al. (2013) (27)	93 (77/16) 47:46	cTACE (EPI, MMC, FUDR)	Fuzheng Jiedu decoction (扶正解毒汤)	12 weeks	Overall survival at 0.5-, 1-, 2-, 3-year Number of CR, PR
Li et al. (2013) (28)	105 (76/29) 43:62	cTACE (5-FU, MMC, THP)	Brucea javanica oil solution (鸦胆子)	8 weeks	Overall survival at 0.5-, 1-, 2-, 3-year
Deng et al. (2014) (29)	80 (51/29) 42:38	cTACE (5-FU, MMC)	Jianpi Yigan decoction (健脾益肝汤)	12 weeks	Overall survival at 0.5-. 1-, 3-year Number of CR, PR Quality of life (KPS)
Lei et al. (2014) (30)	49 (34/15) 32:17	Unknown	Pingwei Xiaoliu decoction (平胃消瘤汤)	12 weeks	Overall survival at 0.5-, 1-, 2-year
Li et al. (2015) (31)	72 (63/9) 36:36	cTACE (5-FU, DDP, EPI, MMC)	Yipi Yanggan decoction (益脾养肝方)	Unknown	Overall survival at 1-year
Wang et al. (2015) (32)	158 (98/60) 78:80	cTACE (5-FU, L-OHP)	Herbal decoction*	6 weeks	Overall survival at 0.5-, 1-, 3-year Number of CR, PR
Zhu et al. (2015) (33)	67 (47/20) 35:32	cTACE (5-FU, ADM, CBP, DDP, EPI, MMC)	Taohong Siwu decoction (桃红四物汤)	Unknown	Overall survival at 0.5-, 1-year Number of CR, PR
He et al. (2016) (34)	60 (54/6) 30:30	cTACE (5-FU, EPI, MMC)	Qingre Jiedu mixture (清热解毒汤)	8 weeks	Overall survival at 0.5-, 1-year Number of CR, PR
Kou et al. (2016) (35)	68 (50/18) 34:34	cTACE (5-FU, EPI, DDP)	Bazhen decoction (八珍汤)	8 weeks	Overall survival at 1-, 2-year Quality of life (KPS)
Liu et al. (2016) (36)	106 (68/38) 53:53	Unknown	Yipi Yanggan decoction (益脾养肝方)	60 weeks	Overall survival at 1-, 2-, 3-year
Zhong et al. (2016) (37)	160 (127/33) 80:80	Unknown	Herbal decoction*	4-6 weeks	Overall survival at 1-, 3-year Number of CR, PR
Li et al. (2017) (38)	78 (62/16) 40:38	cTACE (5-FU, DDP, THP)	Baoyuan decoction and Xiaoyao powder (保元湯合逍遥散方加減)	15 weeks	Overall survival at 1-, 2-year
Liu et al. (2017) (39)	50 (37/13) 25:25	cTACE (5-FU, CBP, EPI)	Yipi Yanggan decoction (益脾养肝方)	4.5-5.5 weeks	Overall survival at 0.5-, 1-year Number of CR, PR
Pan et al. (2017) (40)	62 (54/8) 31:31	cTACE (CBP, MMC, THP)	Shentao Ruangan tablet (参桃软肝方)	4-48 weeks	Overall survival at 0.5-, 1-year Number of CR, PR

(Continued)

TABLE 2 Continued

First author (year)	N. of participants (M/F) HM+T:T-only	TACE type (chemotherapeutic drugs)	Herbal medicine (Chinese)	Duration of herbal medicine	Outcome measurements
Song et al. (2017) (41)	80 (48/32) 40:40	cTACE (CBP, MMC, THP)	Wenyang Jiedu formula (温阳解毒汤)	12 weeks	Overall survival at 0.5-, 1-, 2-year Number of CR, PR
Wu Mei et al. (2017) (42)	74 (66/8) 37:37	Unknown	Xiaoliu powder (消瘤散)	12 weeks	Overall survival at 0.5-, 1-year Quality of life (KPS) Number of CR, PR
Wu Yunan et al. (2017) (43)	117 (70/47) 62:55	cTACE (EPI, LOB)	Bielong Ruangan decoction (鳖龙软肝汤)	36 weeks	Overall survival at 1-year Number of CR, PR
Xiao et al. (2018) (44)	364 (311/53) 180:184	cTACE (MMC, THP)	Jiedu granule (解毒颗粒)	24 weeks	Overall survival at 1-, 2-, 3-year
Cui et al. (2019) (45)	74 (42/32) 37:37	cTACE (Unknown)	Herbal decoction*	8 weeks	Overall survival at 0.5-, 1-year
Yang et al. (2021) (46)	291 (243/48) 144:147	cTACE (DDP, THP)	Fuzheng Jiedu Xiaoji formula (扶正解毒消积方)	12 weeks	Overall survival at 1-year

T; TACE, HM; Herbal medicine, CR; complete response, PR; partial response, AFT; α-fetoprotein, KPS; Karnofsky performance status, 5-FU; 5-Fluouracil, DDP; Cisplatin, THP; Pirarubicin, EPI; Epirubicin, L-OHP; Oxaliplatin, ADM; Doxorubicin, MMC; Mitomycin, GEM; gemcitabine, FUDR; floxuridine, CBP; Carboplatin, LOB; Lobaplatin. * The case where only the composition was presented without the specific name of the herbal medicine is indicated.

participants) were Child–Pugh score A. TACE had significant survival advantages compared to supportive care (21.2 vs. 14.5 months for 4 years of observation time) for patients with late-stage HCC (53); thus, the evaluation of the adjuvant effects of herbal medicine are necessary. As for the types of TACE, novel treatment of chemoembolization with drug-eluting beads (DEB-TACE) has been introduced to reduce drawbacks of conventional TACE (c-TACE) and to improve the overall results (54). However, 21 studies except 4 RCTs not described the types of TACE used cTACE in this systematic review (Table 2).

Patients with HCC suffer from various symptoms, such as abdominal pain, diarrhea, nausea, vomiting, jaundice, cholangitis, and fever (55). Surgical resection or TACE can cause pain or discomfort and deteriorate the quality of life (56). In our results, the adjuvant treatment of herbal drugs improved the quality of life after treatment by 10.6 out of 100 points compared to the TACE-alone group. This finding is similar to the result of one article that reported quality of life improvements of 10.0 out of 100 points in three-dimensional conformal radiotherapy, which is typically used for adjuvant therapy with TACE (57). Our study supported that herbal medicine could improve the quality of life by relieving symptoms when combined with TACE. On the other hand, hepatic fibrosis is a crucial factor in determining the prognosis of HCC patients, and hepatic fibrosis progresses gradually and leads to fatal outcomes (58). However, there is no optimal therapeutic for liver fibrosis to date (59). Herbal medicines have been investigated as potential treatments for liver fibrosis due to their anti-inflammatory and antiviral properties (60). For example, Chunggan syrup (CGX), a standardized herbal formula in Korea, improved liver fibrosis, as assessed by the decreases in liver stiffness measurement score, in a clinical trial (61). In another trial, oxymatrin, extracted from *Sophora alopecuraides* L., showed a significant antifibrotic effect (with a total effective rate of 48% vs. 4%

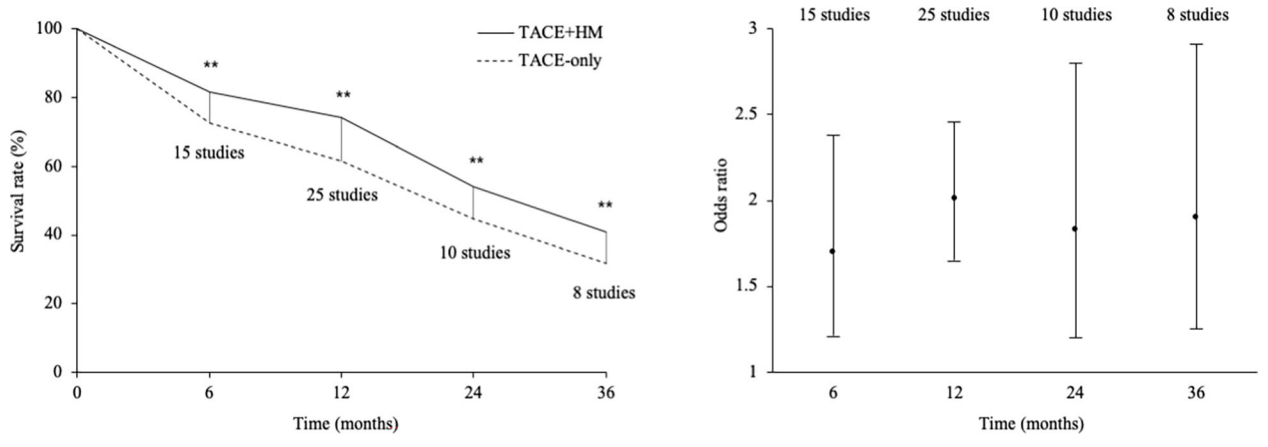

FIGURE 2
Survival rate and odds ratio at 6, 12, 24, and 36 months. ** indicated that P < 0.05.

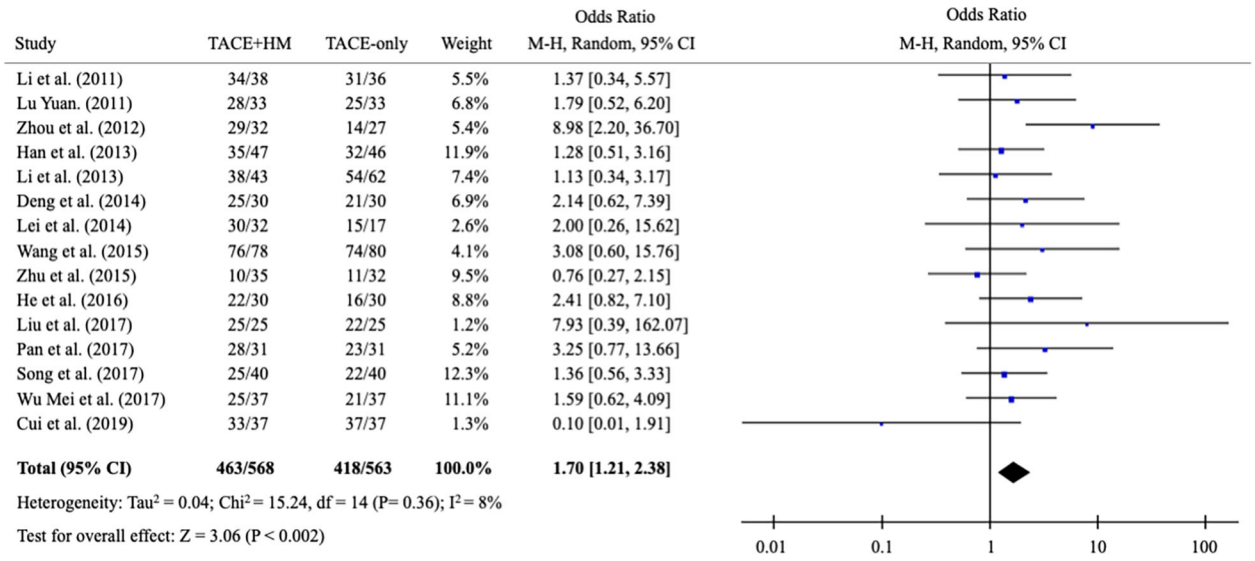

FIGURE 3
Meta-analysis of overall survival at 6-month.

compared to placebo after 24 weeks of administration) (62). These antifibrotic actions may contribute to survival benefits in patients with HCC treated by TACE. Besides antifibrotic properties, there would be other mechanisms corresponding to adjuvant effects of herbal drugs on TACE, we however currently cannot identify them from present data.

In this review, mostly different kinds of herbal medicine were used in 25 studies, except for in 3 of the patients (Supplementary Table 1), and the compositions of these therapies were also diverse (Supplementary Table 2). The heterogeneity of the herbal medicines was the main limitation of this study, which makes it difficult to clarify the interaction between herbal medicine and TACE, and their

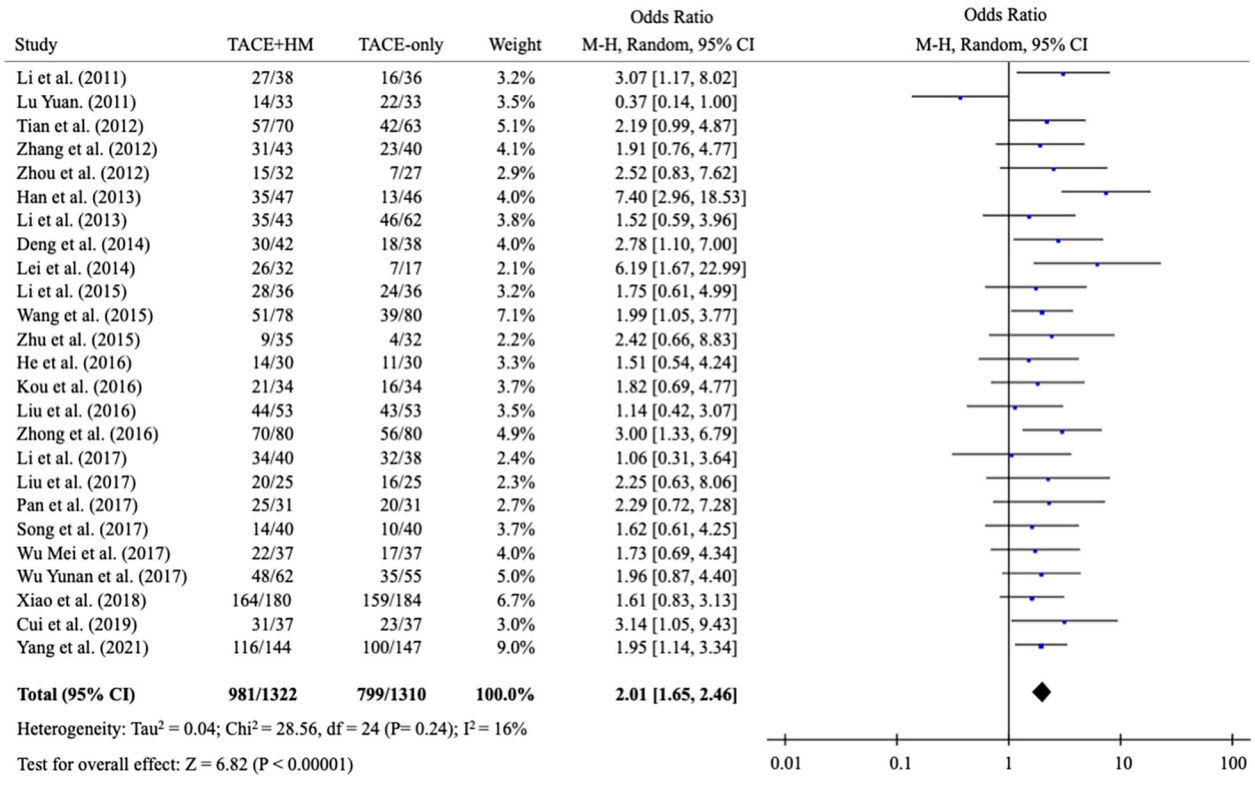

FIGURE 4
Meta-analysis of overall survival at 12-month.

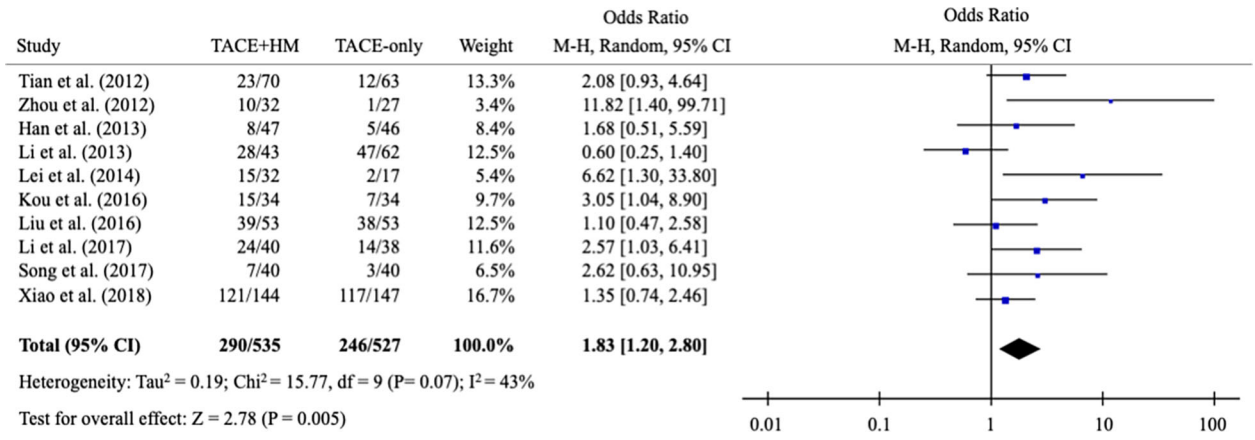

FIGURE 5
Meta-analysis of overall survival at 24-month.

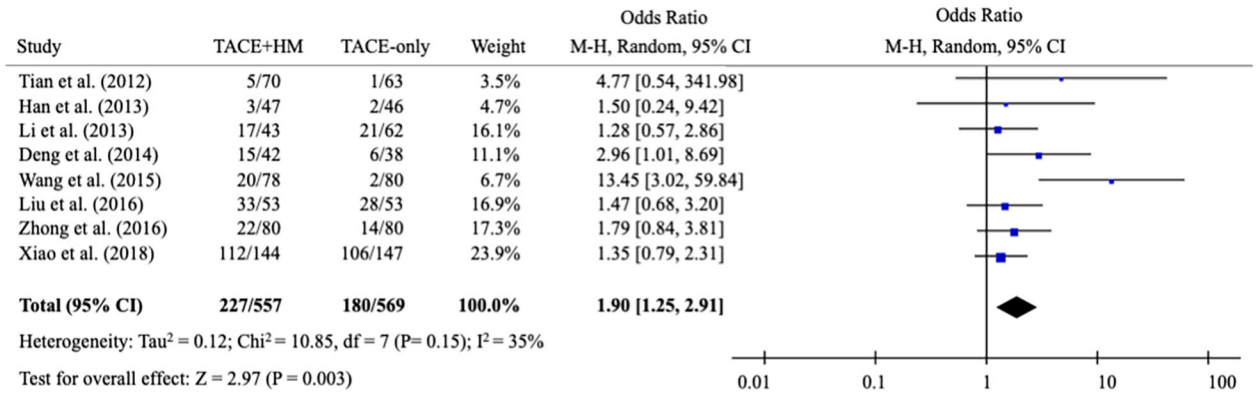

FIGURE 6
Meta-analysis of overall survival at 36-month.

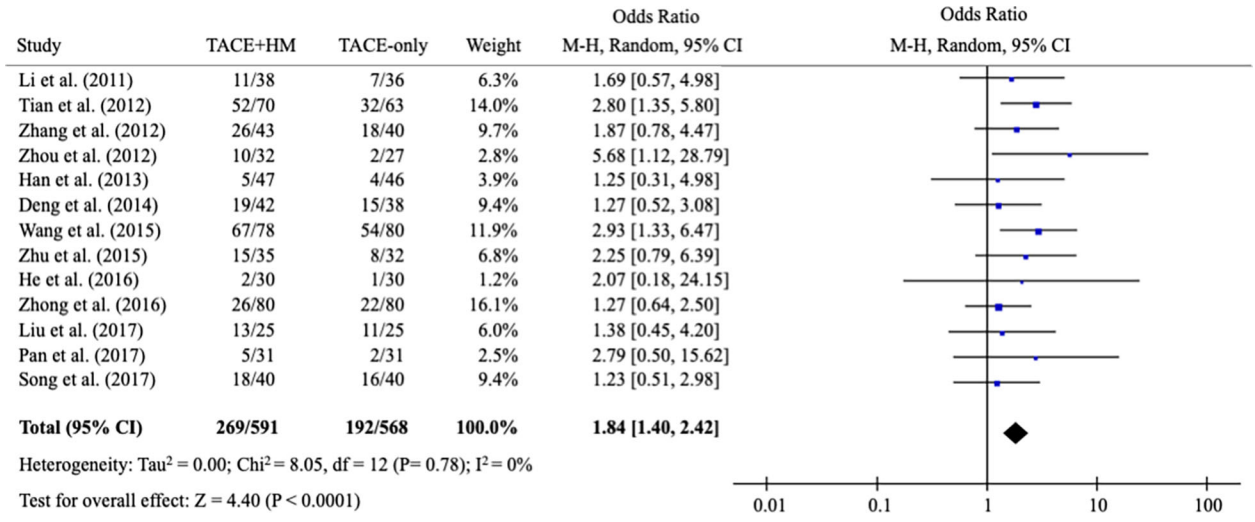

FIGURE 7
Meta-analysis of the number of complete response/partial response.

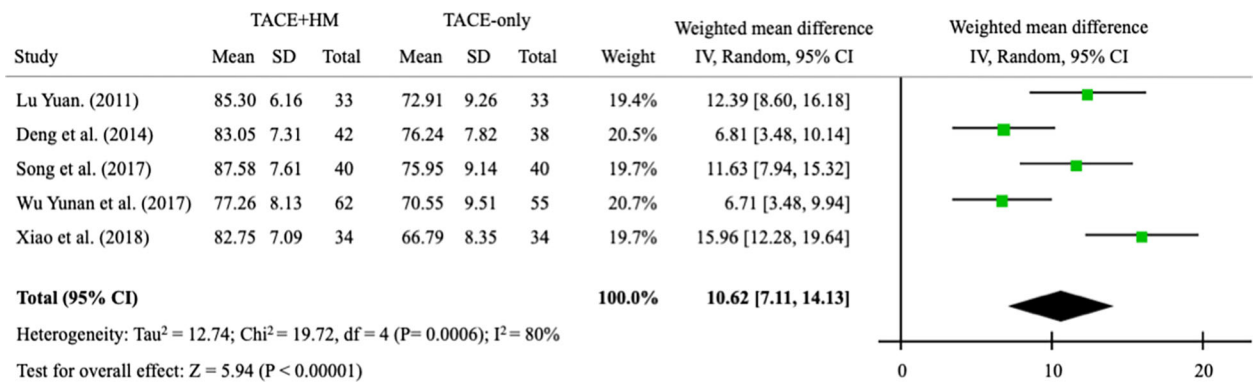

FIGURE 8
Meta-analysis of performance status (Karnofsky performance status score).

corresponding mechanisms. Other limitations would include the unsatisfactory initial data from relatively poorly designed clinical trials and the possibility of publication bias due to only a very few studies reporting negative outcomes. To strengthen the clinical evidence for the adjuvant efficacy of herbal medicine on TACE therapy to treat HCC patients, further strictly designed clinical trials should be performed that have standardized herbal remedies. Herbal drugs have been adopted worldwide, but concerns regarding their safety have arisen (63). Regarding the adverse effects of combination therapy on HCC, the present data did not show any notable frequency compared to only TACE therapy.

In conclusion, this systematic review and meta-analysis showed survival benefits in patients with HCC by combined treatment with herbal medicine and TACE. The adjuvant effect of herbal drugs on TACE needs to be further evaluated by well-designed RCTs in the future.

Data availability statement

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

Author contributions

H-MO: wrote the main manuscript text, and conducted statistical analysis; E-JK, H-RB: contributed to the data collection and manuscript preparation including revision process; J-HC, C-GS: supervised the manuscript; N-HL: supervised the manuscript, and directed final version of all contents. All authors reviewed and approved this manuscript.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1106827/full#supplementary-material

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Effect of HBsAg expression in liver tissue on prognosis of hepatocellular carcinoma after minimally invasive interventional therapy

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Background: The aim of this study was to investigate the association between pathologic markers and prognosis in patients with hepatocellular carcinoma who received transcatheter chemoembolization combined with locoregional ablation therapy.

Methods: This retrospective study included 111 hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC). All patients underwent transcatheter arterial chemoembolization (TACE) combined with locoregional ablation therapy, and received core needle biopsy before therapy in Beijing You 'an Hospital affiliated to Capital Medical University from January 1, 2013 to December 31, 2016. Demographic, pathological indicators and clinical laboratory data were collected. The cumulative recurrence-free survival (RFS) and overall survival (OS) were calculated and compared by Kaplan-Meier method and Log-rank test, and Cox proportional risk model was used to screen for independent predictors of recurrence and long-term prognosis in HCC patients.

Results: There was a correlation between HBsAg expression in liver tissue and prognosis of HCC patients. Patients with negative HBsAg expression had longer 1-,3- and 5-year RFS rates than positive HBsAg expression (78.3%, 43.5%, 30.4% and 58.5%, 24.5%, 17.0%, P=0.018). Meanwhile,the postoperative 1-,3-and 5-year OS rates of HCC patients in the negative HBsAg expression group were significantly higher than those of HCC patients in the positive HBsAg expression group (100%, 89.1%, 80.4% and 100%, 75.5%, 58.5%, P=0.008).

Conclusions: The prognosis of patients with hepatocellular carcinoma with negative HBsAg expression was better than that with positive HBsAg expression. Accordingly, the expression of the liver HBsAg before combined therapy was a prognostic indicator for OS and RFS. For patients with liver HBsAg positive, follow-up should be strengthened and corresponding intervention measures should be taken to improve prognosis.

KEYWORDS

prognosis, HBsAg, interventional therapy, hepatocellular carcinoma, pathology

1 Introduction

There were 910,000 new cases and 830,000 deaths of hepatocellular carcinoma (HCC) worldwide, it was the sixth most common cancer globally and the third leading cause of cancer-related mortality. In China, HCC has 410,000 new cases and 390,000 deaths, ranking fifth and second in morbidity and mortality and HCC has become a health problem in China that cannot be ignored and has increased the medical burden (1).. HCC is usually developing in the context of chronic liver disease, which is mainly associated with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol intake or the metabolic syndrome. However, due to the low early diagnosis rate and high postoperative recurrence rate of HCC, the long-term prognosis of liver cancer is poor, and the 5-year survival rate is only about 12.1% (2, 3).

Due to the high sensitivity and specificity of computerized tomography(CT) or magnetic resonance imaging(MRI)for HCC detection, the diagnosis of liver cancer in most cases does not depend on pathological examination (4, 5). However, the microenvironment of liver is closely related to the occurrence and development of HCC, as it allows for a definitive diagnosis and provides prognostic information of patients (3). Ablation has similar efficacy to surgical for patients with early-stage HCC (6); and transarterial Chemoembolization (TACE) combined with ablation can effectively reduce the local blood supply of tumors and downstage tumors, and has unique advantages in preventing postoperative bleeding. TACE combined with ablation can make up for the disadvantages of TACE or ablation alone (7).

Liver microenvironment is of great significance for the occurrence and development of hepatocellular carcinoma. Therefore, this study aimed to investigate the predictive value of pathological indicators of HCC patients who received combined therapy.

2 Patients and materials

2.1 Study subjects

This is a retrospective study of 111 patients with HCC who received combination therapy from January 1, 2013 to December 31, 2016 at Beijing Youan Hospital (Beijing, China). Most of the patients were early-stage small HCC and all initial treatment patients. For the subsequent diagnosis and treatment plan and prognosis, all patients voluntarily underwent needle biopsy. Biopsy is generally performed under the guidance of ultrasound. Contraindications for percutaneous liver biopsy mainly include patients with bleeding tendency, patients with severe cardiopulmonary disease, massive ascites, severe extrahepatic obstructive jaundice, lack of consciousness, inability to cooperate, suspected hemangioma or other vascular tumors, and suspected echinococcus cyst in the liver. All patients participating in the study were required to meet the following inclusion criteria: 1) age between 18 and 75 years old; 2) the combination of TACE plus ablation is the primary treatment method; 3) Child-Pugh class A or B; 4) no other malignancies that may affect prognosis; 5) all patients underwent core needle biopsy before combined therapy; and 6) HBV-associated HCC. The exclusion criteria were described below: 1) imaging evidence of invasion of the main branches of the portal/hepatic veins; 2) presence of extrahepatic metastases; 3) severe coagulation disorders; 4) incomplete ablation; 5) secondary liver cancer; 6) co-infection with HCV; and 7) missed follow-up examinations Figure 1.

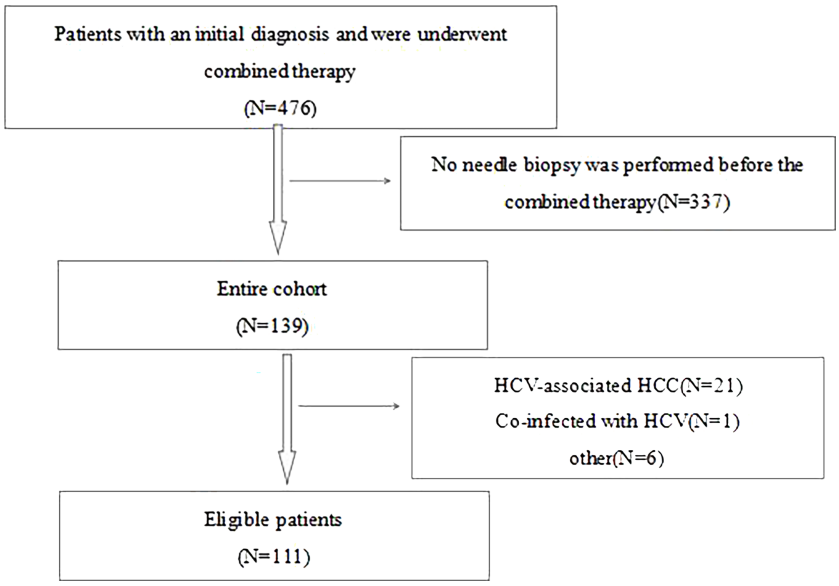

FIGURE 1
Flowchart of study participants. HCC, hepatocellular carcinoma; hepatitis B virus; HCV, hepatitis C virus.

Demographic information, pathological indicators and clinical laboratory data were collected: 1) demographic and etiology indicators, such as age, sex, history of hypertension and somking, serum HBsAg; 2) tumor-related indices, such as the number and size of tumors, and alpha-fetoprotein (AFP) level; 3) liver function indices, including cirrhosis, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum bilirubin (TBIL), serum albumin, globulin, and γ-glutamyl transpeptidase(γ-GT); 4) routine blood examinations, such as neutrophil count (NEU), lymphocyte count (LYM), platelet count (PLT); 5) blood coagulation indicators: including prothrombin time (PT), prothrombin activity (PTA), fibrinogenic (Fib); and 6) pathological indicators: Ki67, P53, HBsAg, Glypican-3 (GPC3), the degree of tumor differentiation. The study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Ethics Committee of You'an Hospital in Beijing. Information on these patients was kept confidential. As a minimal risk study, we dropped the requirement for informed consent.

2.2 Therapeutic methods

Combined therapy was performed by three qualified radiologists and hepatologists with more than 5 years of experience. The femoral artery was punctured using a modified Seldinger method, in which a microcatheter was inserted into the supplying artery of the tumor and doxorubicin (Pfizer, USA) and lipiodol (Gabcod, France) were injected. The interruption of blood flow in the tumor supplying artery was considered complete embolization.Local ablation was performed within 2 weeks after TACE. After the patient has underwent local anesthesia,the procedure is performed percutaneously by hepatologists under the guidance of triphasic computed tomography (CT) or magnetic resonance imaging (MRI). According to the number and size of tumor, overlapping ablation, multi-site ablation and fractional ablation were performed respectively. To ensure complete ablation, a safe distance of 0.5-1.0cm should be maintained around the tumor.

In order to ensure complete ablation of large tumors and multiple tumors, we use the combined treatment of TACE plus ablation, first reducing the target lesion by TACE to facilitate the subsequent complete ablation.On the one hand, TACE can block the blood supply and mark the tumor; on the other hand, TACE is beneficial for subsequent ablation; ablation therapy can further inactivate residual lesions, and ablation treatment is a minimally invasive, efficient and reproducible treatment, so for patients difficult to complete primary ablation, repeated ablation is used to achieve complete ablation.

2.3 Follow-up

Patients follow-up were performed on outpatient clinic. Follow-up consisted of physical examination, blood tests, and imaging examination, which included abdominal ultrasound every 3-6 months and ontrast-enhanced CT/MRI every 6 months. The follow-up involved a physical examination and blood tests, as well as imaging, included an abdominal ultrasound every 3–6 months and contrast-enhanced CT/MRI every 6 months. Recurrence was defined as intrahepatic local progression, distal intrahepatic recurrence and extrahepatic metastases. RFS was calculated as the time between the date of ablation and the patient's first evidence-based recurrence or death in patients without evidence of disease recurrence, whereas OS was defined as the time between the date of ablation and tumor-related death or the date of the last visit. The cut-off date for this study is July 1, 2020. Patients were treated with radiofrequency ablation or TACE when they were found to have tumor recurrence. Contrast-enhanced CT and/or MRI is used to determine if a patient has recurrence. Recurrence is considered when a patient's imaging shows enhancement of areas within or around the primary tumor.

2.4 Statistical analysis

Data were analyzed using SPSS 26.0 software (IBM, Armonk, NY, USA), and all figures were created by SPSS and Graphpad Prism 8.0(Graphpad software Inc). Continuous variables were expressed as the mean ± standard deviation (SD), and categorical data were presented as the frequency. Univariate and multivariate Cox regression analyses were performed to assess the independent risk factors of prognosis in HCC patients undergoing combined therapy. The RFS and OS rates were calculated with the Kaplan-Meier method, and the differences between groups were compared by using the Log-rank test. Statistical significance was considered when the P value < was 0.05.

3 Results

3.1 Baseline characteristics and follow-up results

The present study consisted of 90 men (81.1%) and 21 women (18.9%) with a mean age of 56 years ± 9 years. Additionally, 27 patients (24.3%) had hypertension, 55 patients (49.5%) were received antiviral therapy before they underwent combined therapy. There were 50 patients (45.0%) who had a history of smoking and 33 patients (29.7%) with a history of drinking. By the end of follow-up, 88 (79.3%) recurred and 43 (38.7%) died. The median follow-up duration was 52.2 (36.4-64.9) months. The 1-,3- and 5-year RFS rates were 60.4% (67/111), 29.7% (33/111),and 20.7%(23/111). Moreover, the 1-, 3-, and 5-year cumulative OS rates were 100%(111/111), 73.0% (81/111) and 61.3% (68/111), respectively. There were differences in age (P=0.040) and lymphocyte count (P=0.015) between the recurrence group and the non-recurrence group (Table 1).

TABLE 1 Comparison of data between recurrent and non-recurrent HCC patients.

Variables	Total	Non-Recurrence	Recurrence	P
Gender, male/female	90/21	20/4	70/17	0.981
Age,≤60 years/>60 years	73/38	20/4	53/34	**0.040**
Hypertension,yes/no	27/84	9/15	18/69	0.089
Antiviral,yes/no	51/60	11/13	40/47	0.990
Smoking,yes/no	50/61	11/13	39/48	0.930
Drinking,yes/no	33/78	6/18	27/60	0.567
Family,yes/no	54/57	13/11	41/46	0.541
Cirrhosis,yes/no	86/25	20/4	66/21	0.438
Tumor size,≤3cm vs>3cm	57/51	12/12	45/39	0.757
Tumor number, solitary/multiple	78/26	19/5	59/21	0.591
AFP,≤7ng/mL vs>7ng/mL	49/62	9/15	40/47	0.459
Ki67,≤10% vs>10%	63/48	16/8	47/40	0.268
GPC3,Negative/Positive	14/96	0/24	14/72	0.077
P53,Negative/Positive	24/84	6/18	18/67	0.690
Tumor differentiation,poor/middle/well	30/60/20	8/14/2	22/46/18	0.344
HBsAg,Negative/Positive (%)	46/53	12/9	34/44	0.269
ALT (U/L)	45.83 ± 29.43	47.46 ± 33.59	45.14 ± 27.62	0.639
AST (U/L)	35.17 ± 17.75	37.85 ± 22.77	34.43 ± 16.19	0.406
Total serum bilirubin (μmol/L)	17.16 ± 8.41	14.75 ± 6.78	17.82 ± 8.73	0.073
ALB (g/L)	37.76 ± 4.48	38.74 ± 3.78	37.48 ± 4.64	0.225
γ-GT (u/L)	62.20 (38.90,86.20)	64.00 (44.75,81.05)	61.50 (36.20,87.70)	0.788
HBsAg (serum),Negative/Positive	1/106	0/23	1/83	0.785
PLT (10^9/L)	137.25 ± 59.04	124.71 ± 51.79	140.74 ± 60.73	0.241
LYM (10^9/L)	1.29 ± 0.58	1.09 ± 0.39	1.35 ± 0.61	**0.015**
NEU (10^9/L)	4.01 ± 1.89	3.96 ± 1.84	4.02 ± 1.92	0.890
PT	11.94 ± 1.06	11.70 ± 0.77	12.00 ± 1.12	0.134
PTA	92.12 ± 12.67	94.08 ± 9.05	91.57 ± 13.49	0.290
Fib (g/L)	3.13 ± 0.99	2.99 ± 0.91	3.16 ± 1.01	0.456

Bolded values indicates P<0.05, which is statistically significant.

3.2 Indicators that correlate with RFS

Correlations between demographic and pathological indicators and clinical laboratory data and RFS were assessed with univariate and multifactorial analyses. The univariate analysis demonstrated that RFS was significantly associated with age, intrahepatic HBsAg, albumin, total serum bilirubin, PT and PTA. The multivariate analysis showed that intrahepatic HBsAg expression (HR: 1.965; 95% CI: 1.169-3.304) was an independent predictor of HCC recurrence (P<0.05) (Table 2).

3.3 Indicators that correlate with OS

Univariate and multivariate analyses were performed to assess the relationship between demographic, pathological indicators and clinical laboratory data and OS. Univariate analysis showed that OS was significantly correlated with cirrhosis, antiviral, intrahepatic HBsAg expression, GGT, PT and PTA. The multivariate analysis showed that intrahepatic HBsAg expression (HR:2.320;95% CI:1.093~4.925)and antiviral(HR:3.272;95%CI:1.480~7.234) were an independent predictor of HCC survival status (P<0.05) (Table 3).

TABLE 2 Prognostic factors for RFS by Cox proportional hazards regression model.

Variables	Univariate		Multivariate	
	HR (95%)	P value	HR (95%)	P value
Gender	0.983 (0.578-1.673)	0.949		
Age	1.567 (1.012-2.428)	**0.044**	1.161 (0.690-1.954)	0.574
Hypertension	0.731 (0.435-1.228)	0.236		
Antiviral	1.006 (0.699-1.627)	0.766		
Smoking	1.022 (0.668-1.564)	0.919		
Drinking	0.997 (0.631-1.574)	0.989		
Family	0.908 (0.596-1.385)	0.654		
Cirrhosis	1.060 (0.647-1.737)	0.817		
Tumor size	1.039 (0.676-1.597)	0.86		
Tumor number	1.350 (0.815-2.235)	0.244		
AFP	0.933 (0.611-1.424)	0.747		
Ki67	1.128 (0.739-1.722)	0.578		
GPC3	0.698 (0.391-1.246)	0.224		
P53	0.936 (0.556-1.577)	0.804		
Tumor differentiation	1.253 (0.908-1.728)	0.17		
HBsAg	1.716 (1.090-2.701)	**0.02**	1.965 (1.169-3.304)	**0.011**
ALT (U/L)	0.999 (0.992-1.006)	0.781		
AST (U/L)	0.997 (0.985-1.008)	0.572		
Total serum bilirubin (μmol/L)	1.024 (0.999-1.049)	**0.06**	1.028 (0.997-1.061)	0.081
ALB (g/L)	0.956 (0.911-1.005)	**0.075**	1.012 (0.951-1.077)	0.714
γ-GT (u/L)	1.004 (1.001-1.008)	**0.015**	1.004 (0.999-1.008)	0.100
PLT (10^9/L)	1.000 (0.997-1.004)	0.871		
LYM (10^9/L)	1.243 (0.859-1.798)	0.249		
NEU (10^9/L)	0.977 (0.875-1.091)	0.684		
HBsAg (serum)	0.772 (0.107-5.582)	0.798		
PT	1.281 (1.041-1.576)	**0.019**	2.294 (0.929-5.665)	0.072
PTA	0.983 (0.966-1.001)	**0.059**	1.060 (0.985-1.140)	0.122
Fib (g/L)	1.134 (0.919-1.400)	0.242		

Bolded values indicates P<0.05, which is statistically significant.

TABLE 3 Prognostic factors for OS by Cox proportional hazards regression model.

Variables	Univariate		Multivariate	
	HR (95%)	P value	HR (95%)	P value
Gender	0.815 (0.361-1.840)	0.622		
Age	1.423 (0.757-2.676)	0.273		
Hypertension	0.813 (0.374-1.767)	0.601		
Antiviral	1.739 (0.933-3.244)	**0.082**	3.272 (1.480-7.234)	**0.003**
Smoking	1.484 (0.802-2.743)	0.209		

(Continued)

TABLE 3 Continued

Variables	Univariate		Multivariate	
	HR (95%)	P value	HR (95%)	P value
Drinking	1.442 (0.762-2.728)	0.26		
Family	0.870 (0.470-1.609)	0.657		
Cirrhosis	2.443 (0.958-6.232)	**0.062**	1.193 (0.433-3.290)	0.733
Tumor size	0.947 (0.502-1.786)	0.866		
Tumor number	1.187 (0.578-2.440)	0.64		
AFP	1.277 (0.681-2.393)	0.446		
Ki67	1.027 (0.508-1.756)	0.858		
GPC3	0.660 (0.292-1.489)	0.316		
Tumor differentiation	1.172 (0.738-1.862)	0.501		
HBsAg	2.625 (1.254-5.496)	**0.01**	2.320 (1.093-4.925)	**0.028**
ALT (U/L)	0.998 (0.987-1.008)	0.661		
AST (U/L)	1.000 (0.984-1.016)	0.983		
Total serum bilirubin (μmol/L)	1.001 (0.966-1.038)	0.937		
ALB (g/L)	0.931 (0.870-0.996)	**0.039**	0.997 (0.908-1.094)	0.945
γ-GT (u/L)	1.005 (1.001-1.009)	**0.009**	1.004 (1.000-1.009)	0.062
PLT (10^9/L)	0.998 (0.993-1.004)	0.55		
LYM (10^9/L)	1.101 (0.625-1.941)	0.738		
NEU (10^9/L)	0.935 (0.789-1.108)	0.439		
HBsAg (serum)	0.414 (0.057-3.032)	0.385		
PT	1.463 (1.099-1.946)	**0.009**	1.790 (0.461-6.960)	0.400
PTA	0.972 (0.947-0.996)	**0.024**	1.020 (0.914-1.138)	0.728
Fib (g/L)	0.950 (0.694-1.300)	0.747		

Bolded values indicates P<0.05, which is statistically significant.

3.4 Analysis of clinical and prognostic data based on intrahepatic HBsAg expression

To investigate the influence of intrahepatic HBsAg expression on patient prognosis, patients were divided into two groups according to the expression of intrahepatic HBsAg; one group was positive intrahepatic HBsAg expression, and the other one was negative intrahepatic HBsAg expression. Statistical analysis showed that the age (P=0.004), cirrhosis (P=0.040) and neutrophil count (P=0.020) were significant difference between the two group (Table 4; Figure 2).

Kaplan-meier analysis confirmed that positive intrahepatic HBsAg expression was a negative predictor of RFS and OS. The cumulative 1-, 3-, and 5-year RFS rates for patients with negative HBsAg expression after combined therapy were 78.3%, 43.5% and 30.4%; while for patients with positive HBsAg expression were 58.5%, 24.5% and 17.0%, respectively (P=0.018).(Figure 3) Meanwhile, the cumulative 1-, 3-, and 5-year OS rates for patients with negative HBsAg expression after combined therapy the were 100%, 89.1% and 80.4%, while, for patients with positive HBsAg expression were 100%, 75.5% and 58.5%, respectively (P=0.008) (Figure 4).

4 Discussion

The incidence of HCC is very high and increasing in developing countries, especially in China. And its incidence and mortality rates continue to increase (8). It has been reported that even in patients with early-stage (BCLC-0/A), the 5-year recurrence rate is 50-85% (9–13). As a result, HCC has increased the burden of medical care in our country and become a serious health problem (14).

The results of this study suggest that antiviral treatment was an independent risk factor for OS. A number of previously conducted studies indicated that HBV reactivation is the main risk factor for liver cancer recurrence (15–17), postoperative antiviral therapy can reduce viral load and liver inflammation, improve liver function and the prognosis of patients, and reduce HCC recurrence and mortality. The current research showed that antiviral treatment can effectively

TABLE 4 Comparison of clinical data based on intrahepatic HBsAg.

Variables	HBsAg		P
	Negative	Positive	
Gender, male/female (%)	37/9	42/11	0.883
Age,≤60 years/>60 years (%)	37/9	28/25	**0.004**
Hypertension,yes/no (%)	13/33	10/43	0.270
Antiviral,yes/no (%)	20/26	27/26	0.458
Smoking,yes/no (%)	19/27	22/31	0.984
Drinking,yes/no (%)	16/30	14/39	0.366
Family,yes/no (%)	21/25	27/26	0.599
Cirrhosis,yes/no (%)	31/15	45/8	**0.040**
Tumor size,≤3cm vs>3cm (%)	23/23	31/20	0.286
Tumor number, solitary/multiple (%)	35/10	34/14	0.444
AFP,≤7ng/mL vs>7ng/mL (%)	23/23	24/29	0.639
Ki67,≤10% vs>10% (%)	27/19	28/25	0.588
GPC3,Negative/Positive (%)	4/41	10/43	0.159
P53,Negative/Positive (%)	11/35	11/40	0.783
Tumor differentiation,poor/middle/well (%)	15/24/7	13/28/12	0.528
ALT (U/L)	45.64 ± 32.76	44.00 ± 25.92	0.782
AST (U/L)	37.60 ± 23.16	33.78 ± 13.07	0.326
Total serum bilirubin (μmol/L)	18.67 ± 9.01	15.97 ± 7.32	0.108
ALB (g/L)	38.72 ± 4.38	37.16 ± 4.44	0.083
γ-GT (u/L)	61.95 (38.98-83.53)	54.30 (35.85-84.45)	0.700
PLT (10^9/L)	137.32 ± 57.37	135.67 ± 61.13	0.891
LYM (10^9/L)	1.32 ± 0.54	1.28 ± 0.63	0.703
NEU (10^9/L)	4.54 ± 2.08	3.60 ± 1.80	**0.020**
HBsAg (serum)	1/44	0/51	0.469
PT	11.82 ± 1.10	11.94 ± 0.97	0.545
PTA	94.00 ± 13.10	91.85 ± 11.95	0.395
Fib (g/L)	3.16 ± 1.06	3.07 ± 0.90	0.663

Bolded values indicates P<0.05, which is statistically significant.

improve the outcomes of patients who received surgical and ablation therapy while improve the survival rate of patients (18).

HBV infection to the progression of cancer is a multi-step process (19), HBsAg promotes the proliferation of HCC cells through the activation of the Src/pi3k/Akt pathway (20). Chronic inflammation caused by chronic viral infection leads to changes in the liver microenvironment and increases increase the risk of HCC development. The results of this study confirm that intrahepatic HBsAg positive expression is an independent risk factor for predicting OS and RFS in patients who received combined therapy. The study also showed that the OS and RFS of negative express patients were better than those with positive HBsAg expression.

The results of this study showed there was no correlation between HBsAg in serum and HBsAg in liver tissues. This is consistent with the results of the studies reported in previous articles (21). However, the results of the present study indicated that serum HBsAg expression is associated with intrahepatic HBsAg expression, the paper also suggested that not all serum HBsAg expression was consistent with intrahepatic HBsAg expression (22), the negative correlations observed between low liver HBsAg levels and the increased expression of T- and B cell-activated genes may point toward a limited HBsAg-induced immune exhaustion and enhanced immune control and/or a higher proportion of leukocytes in the livers of these patients. Therefore, for patients with positive intrahepatic HBsAg

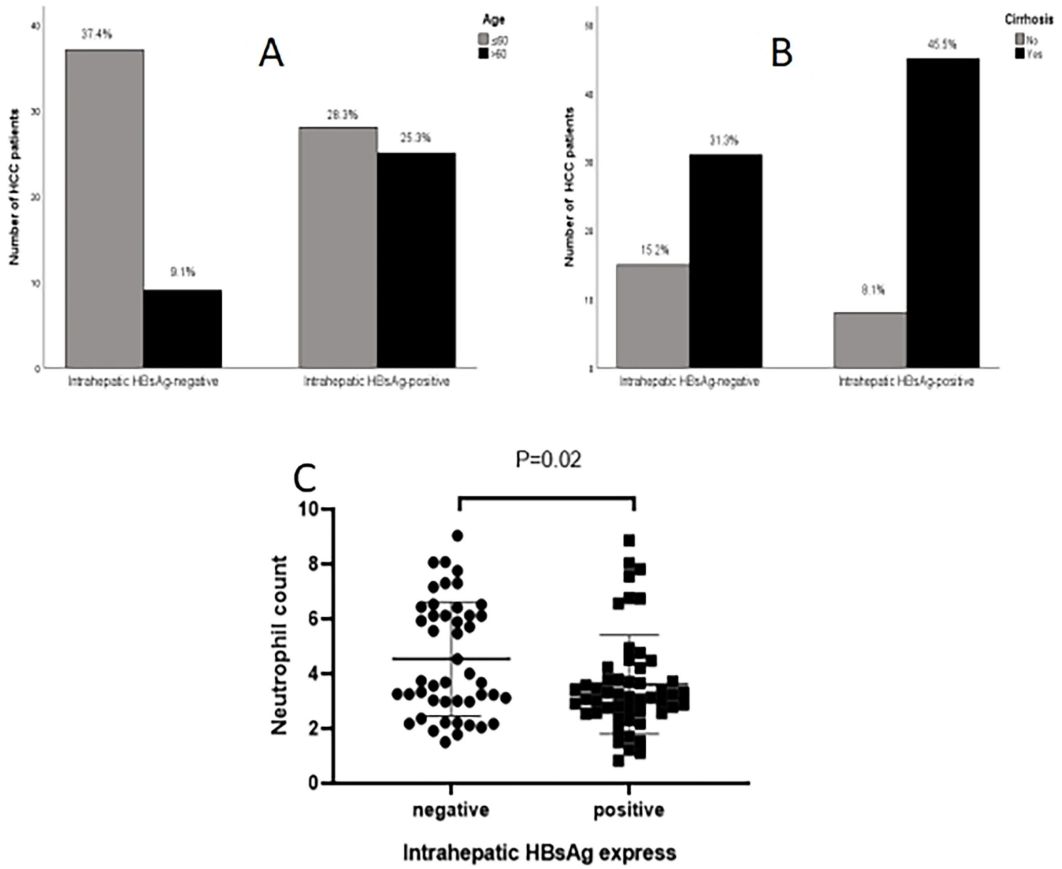

FIGURE 2
Comparison of clinical data based on intrahepatic HBsAg. **(A)** Age; **(B)** Cirrhosis; **(C, D)** neutrophil count.

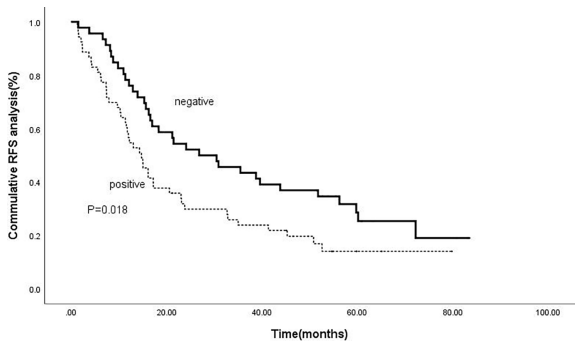

FIGURE 3
Comparison of RFS based on intrahepatic HBsAg. The cumulative 1-, 3-, and 5-year RFS rates for patients with negative HBsAg expression after combined therapy were 78.3%, 43.5% and 30.4%; while for patients with positive HBsAg expression were 58.5%, 24.5% and 17.0%, respectively (P=0.018).

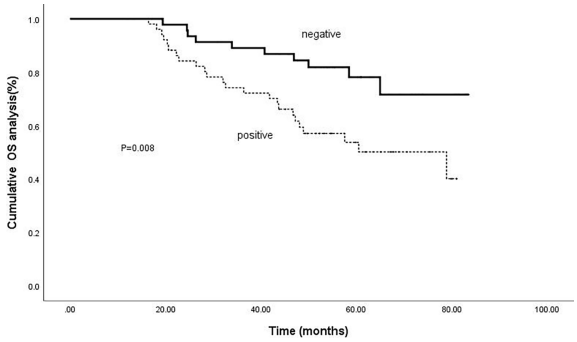

FIGURE 4
Comparison of OS based on intrahepatic HBsAg. The cumulative 1-, 3-, and 5-year OS rates for patients with negative HBsAg expression after combined therapy the were 100%, 89.1% and 80.4%; for patients with positive HBsAg expression were 100%, 75.5% and 58.5%, respectively (P=0.008).

expression, follow-up strategies should be enhanced to monitor tumor progression more closely and to help physicians take timely interventions to decrease the recurrence rate and improve the long-term prognosis of patients.

The prognosis of HCC patients is still poor. Thus, it is crucial to explore the biological indicators that can predict patients' prognosis and make the corresponding clinical decisions according to the patients' situation. In addition, this study is a single-center study while also a small sample study, thus required more centers and a larger sample sizes participation in the validation.

5 Conclusions

Intrahepatic HBsAg positive expression is associated with poor prognosis of HCC patients who underwent combined therapy. Accordingly, for patients with positive HBsAg express in liver tissue, corresponding clinical decisions should be made to improve patients the long-term prognosis of patients.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The data used to support the findings are available from the corresponding author upon request. Requests to access these datasets should be directed to zhangyh@ccmu.edu.cn.

Ethics statement

The study has been approved by the ethics committee of the Beijing You'an Hospital affiliated to Capital Medical University. As a minimum risk study that was in accordance with the Helsinki protocol, the requirement for patients' informed consent was waived by the same ethics committee that approved the study (Beijing You'an Hospital affiliated to Capital Medical University), and all methods were carried out in accordance with relevant guidelines and regulations. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YZ conceived and designed the protocol. JZ and YZ collected the data. BL and QW wrote the manuscript. TM and KL analyzed the data. WG and CY critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Comparative efficacy and safety of molecular targeted agents combined with transarterial chemoembolization in the treatment of unresectable hepatocellular carcinoma: a network meta-analysis

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Objective: At present, several molecular targeted agents(MTAs) combined with transarterial chemoembolization (TACE) have been employed to treat unresectable hepatocellular carcinoma (HCC). In this meta-analysis, we compared the efficacy and safety of different MTAs combined with TACE to enable effective decision-making for the clinical treatment of unresectable HCC.

Methods: Pubmed, Web of Science, EMBASE, and Cochrane Library were retrieved to evaluate the efficacy and safety of different MTAs combined with TACE in cohort studies and randomized controlled trials. The hazard ratios and 95% confidence intervals (CIs) were calculated to investigate the impact of various therapies on overall survival (OS) and progression-free survival. However, the objective response rate (ORR), disease control rate (DCR), adverse events (AEs), and ≥grade-3 adverse events (≥G3-AEs) were calculated using odd ratios and 95% CIs. The node-splitting approach was used to test the heterogeneity. The funnel plot was utilized to analyze the publication bias. Additionally, according to the ranking plots, we ranked various treatments.

Results: A total of 45 studies involving 10,774 patients with 8 treatment strategies were included in our network meta-analysis. Our network meta-analysis showed that apatinib+TACE provided the highest OS (62.2%), ORR (44.7%), and DCR (45.6%), while and lenvatinib+TACE offered the best PFS (78.9%). Besides, there was no statistically significant difference in AEs and ≥G3-AEs among treatment options.

Conclusion: Apatinib+TACE demonstrated the best OS, ORR, and DCR with no additional AEs and ≥G3-AEs. Therefore, for the treatment scheme of MTAs combined with TACE, apatinib+TACE may be the best option for patients with unresectable HCC.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42023388609.

KEYWORDS

transarterial chemoembolization, molecular targeted agents, hepatocellular carcinoma, network meta-analysis, systematic review

1 Introduction

As one of the most prevalent kinds of cancer, primary liver cancer (PLC) incidence rate and mortality rank sixth and third globally, respectively (1). Hepatocellular carcinoma (HCC) accounts for 75% to 95% of PLC cases (1). Features of HCC include insidious onset, lengthy latency, and swift progression. Patients are frequently diagnosed at an advanced stage, making them miss out on the best opportunity for surgery (2). The diagnosis of advanced HCC is found in patients who do not follow the recommended monitoring plan according to the guidelines. According to the guidelines, they should better accept different treatment strategies based on the number and size of HCC. Meanwhile, the median survival of advanced HCC is under one year, making it a significant global health problem (3).

For unresectable HCC (uHCC), the available treatment options mainly include transarterial chemoembolization (TACE), transarterial radioembolization (TARE), liver transplantation, stereotactic body radiation therapy (SBRT), targeted therapy, and immunotherapy (4). Due to its safety, efficacy, minimally invasive nature, and repeatability, TACE has been included as a first-line treatment in the non-radical treatment of HCC which cannot be surgically resected (5). TACE is mainly used to achieve the therapeutic purpose by injecting chemotherapy drugs into the tumor supply arteries and then blocking the above arteries with embolic materials. However, after TACE, the local hypoxia of the tumor blood supply artery will disturb the tumor microenvironment, leading to the upward regulation of hypoxia-inducible factor-1 (HIF-1), which upregulates vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), further increasing tumor angiogenesis (6). Tumor neovascularization forms collateral circulation with other intrahepatic vessels, causing local recurrence and metastasis (7).

Over the past decades, the molecular mechanism of the onset and development of liver cancer has gradually become known through the continued exploration of molecular cell biology. The above progress provides a theoretical basis for the emergence of more molecular targeted agents (MTAs) which inhibit anomalous molecular targets (8). Tumor angiogenesis produced by ascending regulation of VEGFR and PDGFR is the primary cause of tumor spread and relapse following TACE. MTAs can inhibit the PFGF and VEGFR pathways, preventing tumor neovascularization. Meanwhile, molecular targeted therapy reduces tumor growth and differentiation by disrupting tumor signal transduction pathways, resulting in apoptosis and destruction of tumor cells. The Wnt/β-Catenin pathway, Ras/Raf/MAPK pathway, PI3/AKT/mTOR pathway, JAK/STAT pathway, Ubiquitin Proteasome pathway, and IGF1/IGF1R pathway are the principal targeted pathways for the therapy of HCC (8). Growth factors, signaling molecules, cyclins, apoptotic regulators, and chemicals that encourage angiogenesis in the route are among the compounds that targeted medications target (9). Different MTAs act on various transduction pathways, depending on the targets they are meant to affect. By obstructing signals that encourage cancer cell development, disrupting the control of the cell cycle, or inducing cell death, MTAs destroy cancer cells (10). Both TACE and MTAs have anti-tumor properties. At the same time, MTAs can reverse the tumor recurrence and metastasis caused by TACE treatment, which promotes tumor angiogenesis. Consequently, there is an increasing trend in clinical practice to combine TACE and MTAs to treat uHCC.

As more and more MTAs arrive on the market, so does the number of MTAs that TACE can jointly choose. However, due to the lack of head-to-head comparison of TACE in combination with MTAs, the ideal strategy for TACE in combination with MTA still needs to be discovered. Consequently, a network meta-analysis (NMA) was performed to compare the efficacy and safety of various MTAs combined with TACE.

2 Materials and methods

2.1 Protocol and registration

This NMA was registered in PROSPERO (CRD42023388609). Additionally, the study was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.2 Literature search strategy

We systematically searched Pubmed, Web of Science, EMBASE, and Cochrane Library from the date of establishment to January 4, 2023. The paramount search terms were "liver neoplasms", "chemoembolization, therapeutic", "sorafenib", "sunitinib", "brivanib", "anlotinib", "apatinib", "orantinib", "lenvatinib" along with their synonyms. The detailed search strategy is outlined in Supplementary Table 1.

2.3 Study inclusion and exclusion criteria

Studies were included in this NMA if they met the following inclusion criteria: (a) Patients: adults who were at least 18 years old diagnosed with uHCC; uHCC patients did not receive systematic treatment prior to receiving MTA combined with TACE or TACE alone; no additional treatment was administered during the studies, including radiofrequency ablation, percutaneous ethanol injection or iodine-125 seed implantation. (b) Intervention: TACE as monotherapy therapy or in combination with several MTAs. (c) Comparison: studies that compared the outcomes of various interventions in treating uHCC. (d) Outcomes: efficacy indicators included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR); safety indicators included the incidence of adverse events (AEs) and ≥grade-3 adverse events (≥G3-AEs). (e) Study design: randomized controlled trials (RCTs) and cohort studies.

The following studies were eliminated from this NMA: case reports, reviews, case-control studies, editorials, and studies with insufficient data.

2.4 Data extraction and quality assessment

After determining the RCTs and cohort studies to be included in this study, two researchers (BC and ZL) independently extracted data. Any differences were resolved by a third researcher (JL). The following data were extracted: first author, publication year, region, treatment measures, sample size, gender, age, and disease characteristics.

We applied two quality evaluation tools to evaluate two types of studies. For cohort studies, we applied the Newcastle-Ottawa scale, which evaluated cohort studies through eight items. The eight items mentioned above consisted of the representativeness of the exposure cohort, the selection of the non-exposed cohort, the determination of the exposure, the absence of the disease to be studied at the beginning of the study, the comparability of the exposure cohort and the non-exposed cohort, the measurement method of the results, whether the follow-up time was long enough and the integrity of the follow-up. Apart from the item of comparability between exposed and non-exposed cohorts, which could be rated up to two stars, other items could be rated up to one star, with a total score of nine stars. For RCTs, the Cochrane's Risk of Bias Tool, recommended by the Cochrane Handbook, was used to investigate sources of bias from seven dimensions. The seven dimensions were described in terms of six aspects, namely, selection bias, implementation bias, measurement bias, follow-up bias, reporting bias, and other biases. Each dimension was judged and divided by low, high, and unclear risk of bias.

2.5 Statistical analysis

R version 3.6.1 and StataMP 14.0 were used to analyze relevant data. We conducted a Bayesian NMA employing a random effect model to compare directly or indirectly the efficacy and safety of each treatment included in the study. To obtain the posterior distribution, we established three independent Markov chains for each outcome measure. The number of iterations per chain was set at 50,000, with the first 5,000 being considered burn-in samples. The model's convergence was assessed employing Brooks-Gelman-Rubin plots and trace plots.

For OS and PFS, the pooled hazard ratio (HR) and 95% confidence intervals (CIs) were used for comparison. For ORR, DCR, AEs, and ≥G3-AEs, the pooled odds ratio (OR) and 95% CIs were used for comparison. We extracted data from Kaplan-Meier plots for those studies that did not offer HR values utilizing Engauge Digitizer version 11.3 software. The ranking probability was used to evaluate the ranking of each treatment measure. The node-splitting approach was used to determine if direct or indirect comparisons were coherent. Funnel plots were used to assess whether the included study had publication bias. If the funnel plot was symmetrical, it indicated no publication bias. Otherwise, there may be publication bias. Two-tailed $P<0.05$ was deemed statistically significant.

3 Results

3.1 Search results and quality assessment

In our selected database, 9,370 studies were initially identified, and another study was obtained through other means. After removing 2,966 duplicate articles, 6,305 articles were abstracted and screened. Following the preliminary screening, 777 articles met the evaluation criteria. Subsequently, after excluding 607 systematic reviews or case reports, 121 non-human trials, 1 article with incomplete data, and 3 articles receiving other treatments, a total of 10 RCTs (11–20) and 35 cohort studies (21–55) were included for NMA. The literature screening process is illustrated in Figure 1.

In our NMA, a total of 7 MTAs+TACE treatment schemes were included, namely: sorafenib+TACE (Sora+TACE), lenvatinib+TACE (Lenv+TACE), sunitinib+TACE (Suni+TACE), brivanib +TACE (Briv+TACE), anlotinib+TACE (Anlo+TACE), apatinib +TACE (Apat+TACE) and orantinib+TACE (Oran+TACE). There were 10,774 HCC patients in our 45 included studies. Among them, 19 studies (11–14, 21–35) were about the comparison of Sora+TACE and TACE monotherapy, 3 studies (36–38) were about the comparison of Lenv+TACE and TACE monotherapy, 11 studies

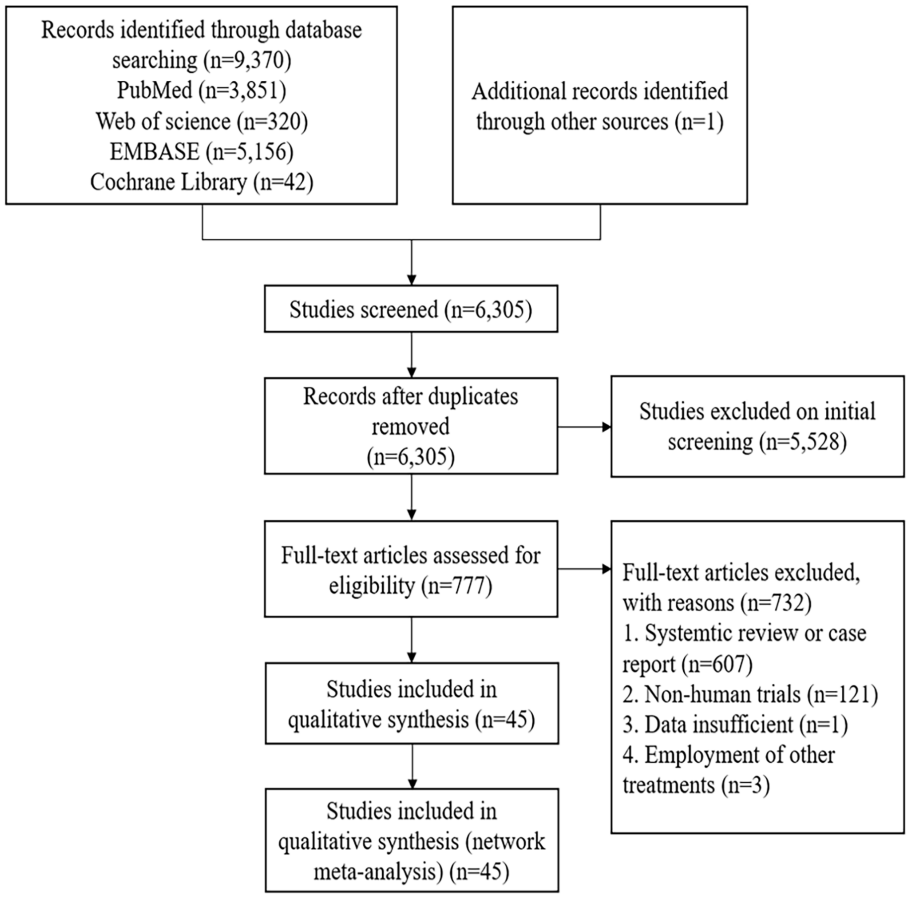

FIGURE 1
Flow chart of the study screening process.

(15, 39–48) were about the comparison of Apat+TACE and TACE monotherapy, 1 studies (49) was about the comparison of Anlo +TACE and TACE monotherapy, 1 study (16) was about the comparison of Briv+TACE and TACE monotherapy, and 2 studies (17, 50) were about the comparison of Suni+TACE and TACE monotherapy, and 3 studies (18–20) were about the comparison of Oran+TACE and TACE monotherapy. Moreover, there were 2 studies (51, 52) on the comparison of Lenv+TACE and Sora+TACE, 2 studies (53, 54) on the comparison of Sora+TACE and Apat+TACE, and 1 study (55) on the comparison of Suni+TACE and Sora+TACE. In the included studies, the patient count was between 42 and 1,719. The age of patients varied between 18 and 87 years. The characteristics of the included study are shown in Supplementary Table 2. The quality evaluation of the included literature is shown in Supplementary Table 3.

3.2 Overall survival

For OS, 8 treatment strategies were documented altogether (Figure 2) and in comparison with TACE monotherapy and Oran+TACE, Apat+TACE, Lenv+TACE, and Sora+TACE demonstrated significant OS benefits (HR 0.62, 95% CI 0.50-0.75; HR 0.60, 95% CI 0.44-0.77; HR 0.68, 95% CI 0.49-0.88; HR 0.66, 95% CI 0.44-0.90; HR 0.78, 95% CI 0.68-0.86; HR 0.75, 95% CI 0.58-0.93) (Figure 3). Moreover, Apat+TACE supplied better OS than Sora+TACE and Suni+TACE (HR 0.80, 95% CI 0.67-0.95; HR 0.69, 95% CI 0.49-0.94). In the light of the ranking plot, Apat+TACE had the highest probability (62.2%) of delivering a better OS, followed by Lenv+TACE (40.6%), Sora+TACE (40.4%) and Anlo+TACE (18.3%) (Figure 4; Supplementary Table 4).

3.3 Progression-free survival

For PFS, 7 treatment strategies were documented altogether (Figure 2). Lenv+TACE and Apat+TACE were significantly ahead of Sora+TACE, Suni+TACE, and TACE monotherapy. Lenv+TACE offered better PFS than Sora+TACE (HR 0.53, 95%CI 0.32-0.88), Suni+TACE (HR 0.50, 95% CI 0.26-0.92), and TACE monotherapy (HR 0.46, 95% CI 0.28-0.73) (Figure 3). Similarly, Apat+TACE provided a better PFS than Sora+TACE (HR 0.69, 95% CI 0.53-0.93), Suni+TACE(HR 0.64, 95% CI 0.40-1.02), and TACE monotherapy(HR 0.60, 95% CI 0.46-0.75). In the light of the ranking plot, Lenv+TACE had the highest probability (78.9%) of providing a superior PFS, followed by Apat+TACE (58.1%),

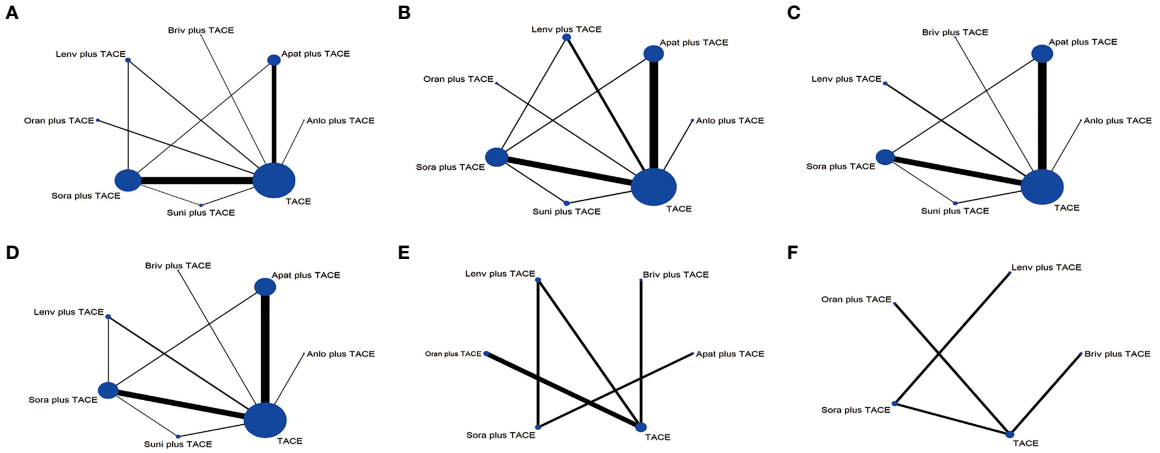

FIGURE 2
Network plots of the comparisons for the network meta-analysis. **(A)** Overall survival. **(B)** Progression-free survival. **(C)** Objective response rate. **(D)** Disease control rate. **(E)** ≥Grade-3 adverse events. **(F)** Adverse events. The size of the circle is proportional to the number of studies. The width of the line is proportional to the study of direct comparison. Lenv plus TACE, lenvatinib+TACE; Briv plus TACE, brivanib+TACE; Apat plus TACE, apatinib+TACE; Anlo plus TACE, anlotinib+TACE; Suni plus TACE, sunitinib+TACE; Sora plus TACE, sorafenib+TACE; Oran plus TACE, Orantinib+TACE.

Oran+TACE (34.4%) and Anlo+TACE(32.7%) (Figure 4; Supplementary Table 4).

3.4 Objective response rate

For ORR, 7 treatment strategies were documented altogether (Figure 2). Compared with TACE monotherapy, Suni+TACE, and Anlo+TACE, Apat+TACE showed a significantly better ORR rate (OR 1.97, 95% CI 1.50-2.66; OR 2.05, 95% CI 1.01-4.04; OR 2.79 95% CI 1.00-8.32) (Figure 3). Sora+TACE was also demonstrated to have a significantly higher ORR rate than TACE monotherapy (OR 1.79, 95% CI 1.34-2.52). Additionally, no significant differences were found among the other treatments. In the light of the ranking plot, Apat+TACE had the highest probability of yielding a higher ORR rate (44.7%), followed by Sora+TACE

A

apatinib+TACE	1.09 (0.78, 1.48)	**1.24 (1.05, 1.5)**	1.3 (0.85, 2.1)	1.44 (0.98, 2.26)	**1.44 (1.07, 2.04)**	**1.6 (1.34, 1.98)**	**1.66 (1.29, 2.28)**
0.92 (0.68, 1.27)	**lenvatinib+TACE**	1.14 (0.88, 1.54)	1.19 (0.75, 2.05)	1.32 (0.86, 2.22)	1.32 (0.93, 2.02)	**1.47 (1.13, 2.04)**	**1.53 (1.11, 2.28)**
0.8 (0.67, 0.95)	0.88 (0.65, 1.13)	**sorafenib+TACE**	1.05 (0.7, 1.63)	1.16 (0.81, 1.75)	1.16 (0.89, 1.55)	**1.29 (1.16, 1.47)**	**1.33 (1.08, 1.74)**
0.77 (0.48, 1.18)	0.84 (0.49, 1.33)	0.96 (0.62, 1.44)	**anlotinib+TACE**	1.11 (0.64, 1.92)	1.11 (0.68, 1.8)	1.23 (0.82, 1.86)	1.28 (0.81, 2.03)
0.7 (0.44, 1.02)	0.76 (0.45, 1.16)	0.87 (0.57, 1.24)	0.9 (0.52, 1.56)	**brivanib+TACE**	1 (0.63, 1.57)	1.11 (0.77, 1.6)	1.15 (0.75, 1.76)
0.69 (0.49, 0.94)	0.76 (0.49, 1.08)	0.86 (0.64, 1.12)	0.9 (0.56, 1.48)	1 (0.64, 1.59)	**sunitinib+TACE**	1.11 (0.86, 1.45)	1.16 (0.83, 1.62)
0.62 (0.5, 0.75)	**0.68 (0.49, 0.88)**	**0.78 (0.68, 0.86)**	0.81 (0.54, 1.22)	0.9 (0.62, 1.3)	0.9 (0.69, 1.17)	**TACE**	1.04 (0.85, 1.28)
0.6 (0.44, 0.77)	**0.66 (0.44, 0.9)**	**0.75 (0.58, 0.93)**	0.78 (0.49, 1.24)	0.87 (0.57, 1.32)	0.87 (0.62, 1.21)	0.96 (0.78, 1.18)	**orantinib+TACE**

B

lenvatinib+TACE	1.3 (0.76, 2.23)	1.53 (0.77, 3.14)	1.78 (0.96, 3.43)	**1.88 (1.13, 3.08)**	**2.02 (1.09, 3.81)**	**2.18 (1.36, 3.6)**
0.77 (0.45, 1.31)	**apatinib+TACE**	1.18 (0.69, 2.08)	1.37 (0.87, 2.24)	**1.45 (1.08, 1.89)**	1.56 (0.98, 2.49)	**1.68 (1.34, 2.18)**
0.65 (0.32, 1.29)	0.85 (0.48, 1.45)	**orantinib+TACE**	1.16 (0.61, 2.22)	1.23 (0.69, 2.01)	1.31 (0.69, 2.47)	1.42 (0.87, 2.34)
0.56 (0.29, 1.04)	0.73 (0.45, 1.15)	0.86 (0.45, 1.63)	**anlotinib+TACE**	1.07 (0.64, 1.58)	1.14 (0.63, 1.99)	1.23 (0.81, 1.85)
0.53 (0.32, 0.88)	**0.69 (0.53, 0.93)**	0.81 (0.5, 1.44)	0.94 (0.63, 1.57)	**sorafenib+TACE**	1.07 (0.72, 1.66)	**1.15 (1.01, 1.47)**
0.5 (0.26, 0.92)	0.64 (0.4, 1.02)	0.76 (0.41, 1.45)	0.88 (0.5, 1.59)	0.93 (0.6, 1.39)	**sunitinib+TACE**	1.08 (0.73, 1.64)
0.46 (0.28, 0.73)	**0.6 (0.46, 0.75)**	0.7 (0.43, 1.15)	0.81 (0.54, 1.23)	**0.87 (0.68, 0.99)**	0.92 (0.61, 1.37)	**TACE**

C

apatinib+TACE	0.91 (0.63, 1.35)	0.87 (0.45, 1.61)	0.59 (0.22, 1.53)	**0.51 (0.38, 0.67)**	**0.49 (0.24, 0.99)**	**0.36 (0.12, 1)**
1.1 (0.74, 1.6)	**sorafenib+TACE**	0.96 (0.49, 1.77)	0.65 (0.23, 1.67)	**0.56 (0.4, 0.74)**	0.54 (0.27, 1.04)	0.39 (0.13, 1.1)
1.15 (0.62, 2.21)	1.04 (0.56, 2.04)	**lenvatinib+TACE**	0.67 (0.23, 2.01)	0.58 (0.33, 1.03)	0.56 (0.24, 1.35)	0.41 (0.13, 1.29)
1.7 (0.65, 4.63)	1.54 (0.6, 4.3)	1.48 (0.5, 4.44)	**brivanib+TACE**	0.87 (0.34, 2.22)	0.83 (0.27, 2.65)	0.61 (0.15, 2.43)
1.97 (1.5, 2.66)	**1.79 (1.34, 2.52)**	1.71 (0.98, 3.02)	1.16 (0.45, 2.94)	**TACE**	0.96 (0.51, 1.88)	0.7 (0.25, 1.93)
2.05 (1.01, 4.14)	1.86 (0.96, 3.64)	1.78 (0.74, 4.19)	1.21 (0.38, 3.65)	1.04 (0.53, 1.97)	**sunitinib+TACE**	0.73 (0.21, 2.39)
2.79 (1, 8.32)	2.54 (0.91, 7.78)	2.44 (0.77, 7.89)	1.65 (0.41, 6.58)	1.42 (0.52, 4.01)	1.36 (0.42, 4.75)	**anlotinib+TACE**

D

apatinib+TACE	0.93 (0.75, 1.15)	0.89 (0.63, 1.23)	0.8 (0.43, 1.44)	0.7 (0.39, 1.25)	0.71 (0.46, 1.05)	**0.7 (0.59, 0.82)**
1.07 (0.87, 1.34)	**sorafenib+TACE**	0.95 (0.69, 1.3)	0.86 (0.47, 1.55)	0.76 (0.42, 1.35)	0.76 (0.51, 1.1)	**0.75 (0.63, 0.88)**
1.13 (0.81, 1.59)	1.05 (0.77, 1.45)	**lenvatinib+TACE**	0.9 (0.47, 1.72)	0.79 (0.42, 1.5)	0.8 (0.49, 1.27)	0.79 (0.59, 1.06)
1.25 (0.69, 2.32)	1.17 (0.64, 2.14)	1.11 (0.58, 2.14)	**anlotinib+TACE**	0.88 (0.39, 1.97)	0.89 (0.44, 1.75)	0.88 (0.49, 1.57)
1.42 (0.8, 2.58)	1.32 (0.74, 2.4)	1.26 (0.67, 2.39)	1.14 (0.51, 2.55)	**brivanib+TACE**	1.01 (0.51, 1.97)	1 (0.57, 1.75)
1.4 (0.96, 2.17)	1.31 (0.91, 1.97)	1.24 (0.79, 2.03)	1.12 (0.57, 2.27)	0.99 (0.51, 1.96)	**sunitinib+TACE**	0.98 (0.69, 1.45)
1.43 (1.21, 1.71)	**1.33 (1.13, 1.58)**	1.26 (0.94, 1.71)	1.14 (0.64, 2.04)	1 (0.57, 1.76)	1.02 (0.69, 1.46)	**TACE**

FIGURE 3
Pooled efficacy indicators estimates of network meta-analysis. **(A)** Pooled hazard ratios (95% confidence intervals) of overall survival. **(B)** Pooled hazard ratios (95% confidence intervals) of progression-free survival. **(C)** Pooled odds ratios (95% confidence intervals) for objective response rate. **(D)** Pooled odds ratios (95% confidence intervals) for disease control rate.

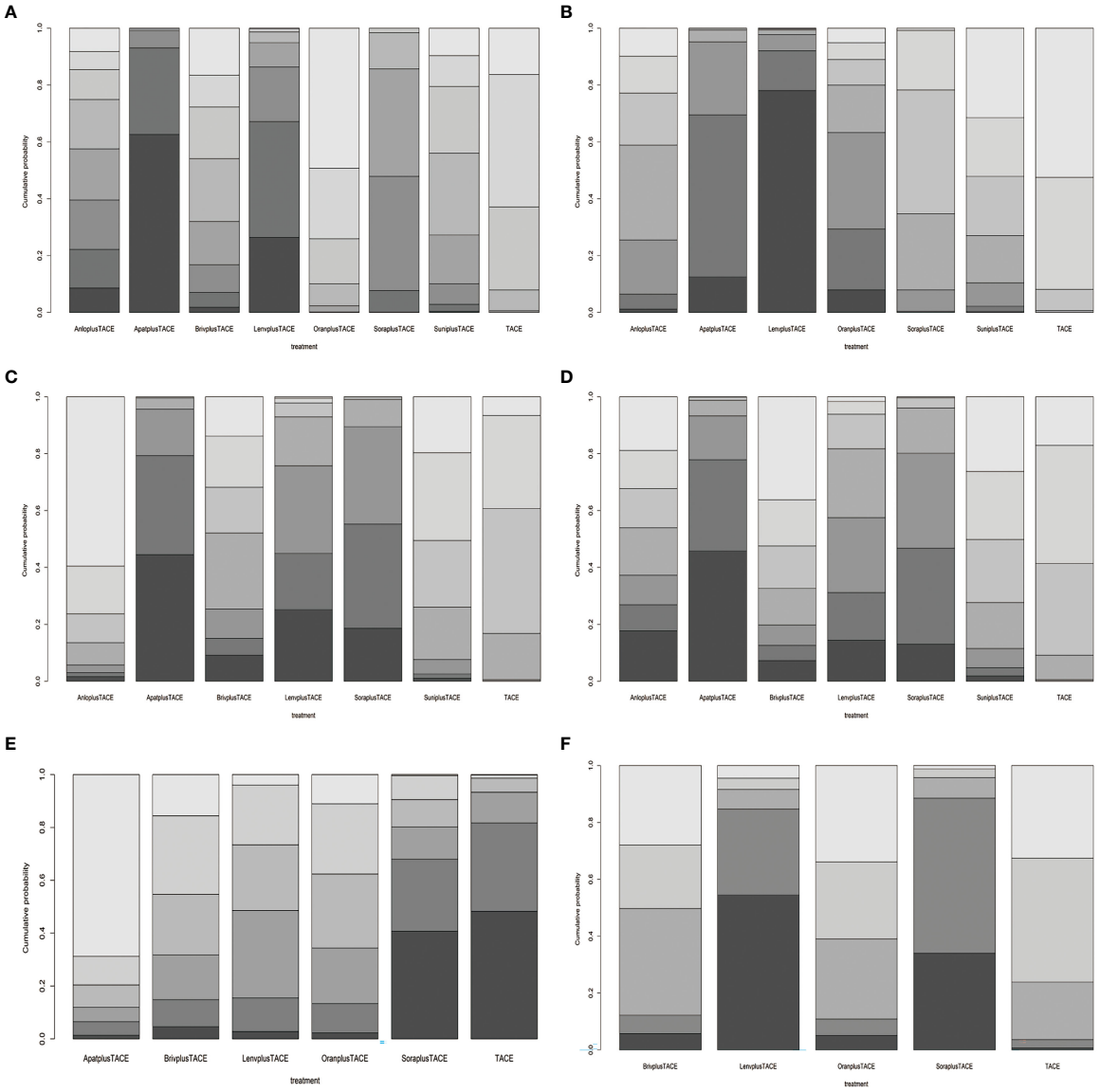

FIGURE 4
Relative rank plots based on probabilities of treatment strategies. **(A)** Overall survival. **(B)** Progression-free survival. **(C)** Objective response rate. **(D)** Disease control rate. **(E)** Adverse events. **(F)** ≥Grade-3 adverse events. Dark to light colors in the bar chart correspond to the ranking from top to bottom. LenvplusTACE, lenvatinib+TACE; BrivplusTACE, brivanib+TACE; ApatplusTACE, apatinib+TACE; AnloplusTACE, anlotinib+TACE; SuniplusTACE, sunitinib+TACE; SoraplusTACE, sorafenib+TACE; OranplusTACE, Orantinib+TACE.

(36.6%), Lenv+TACE (30.7%) and Briv+TACE (32.7%) (Figure 4; Supplementary Table 4).

3.5 Disease control rate

For DCR, 7 treatment strategies were documented altogether (Figure 2). Compared to the remaining six treatment measures, TACE monotherapy showed a lower DCR rate (OR 0.70, 95% CI 0.59-0.82; OR 0.75, 95% CI 0.63-0.88; OR 0.79, 95% CI 0.59-1.06; OR 0.88, 95% CI 0.49-1.57; OR 1.00, 95% CI 0.57-1.75; OR 0.98, 95% CI 0.69-1.45), but most differences were not statistically significant (Figure 3). Whereas there was no significant difference in the DCR of the six treatment strategies when compared with each other, Apat+TACE showed a higher DCR than Sora+TACE (OR 1.07, 95% CI 0.87-1.34), Lenv+TACE (OR 1.13, 95% CI 0.81-1.59), Anlo+TACE (OR 1.25, 95% CI 0.69-2.32), Briv+TACE (OR 1.42, 95% CI 0.80-2.58) and Suni+TACE(OR 1.40, 95% CI 0.96-2.17). In the light of the ranking plot, Apat+TACE had the highest probability of delivering a maximum DCR (45.6%), followed by Sora+TACE (33.7%), Lenv+TACE (26.1%) and Anlo+TACE (16.6%) (Figure 4; Supplementary Table 4).

3.6 ≥Grade-3 adverse events

For ≥G3-AEs, 6 treatment strategies were documented altogether (Figure 2). The various combined therapies did not

significantly differ from one another (Figure 5). TACE demonstrated no statistically significant advantage in the low incidence of ≥G3-AEs while being a relatively safe treatment compared to other combined regimens (OR 0.95, 95% CI 0.27-3.28; OR 0.69, 95% CI 0.29-1.65; OR 0.64, 95% CI 0.35-1.12; OR 0.62, 95% CI 0.27-1.4; OR 0.41, 95% CI 0.09-1.82). In the light of the ranking plot, Apat+TACE was most likely to deliver the highest incidence of ≥G3-AEs (68.8%), followed by Briv+TACE (30.0%). Besides, TACE had the highest probability of delivering the safest treatment (48.2%), followed by Sora+TACE (27.3%) (Figure 4; Supplementary Table 4).

3.7 Adverse events

For AEs, 5 treatment strategies were documented altogether (Figure 2). There was no significant difference between the various treatment measures (Figure 5). Given the ranking plot, Oran+TACE had the highest probability of providing the safest treatment (34.3%), followed by TACE (44.2%). Besides, Sora+TACE was most likely to deliver the highest incidence of AEs (53.4%), followed by Lenv+TACE (53.4%) (Figure 4, Supplementary Table 4).

3.8 Publication bias and inconsistency analysis

The funnel plots of all indicators in the included study were nearly symmetrical, indicating no publication bias (Figure 6). Utilizing the node-splitting method, we found no inconsistency between direct and indirect comparison (Supplementary Table 5).

4 Discussion

So far, TACE combined with MTAs has become an essential approach for treating uHCC. Increasing combined therapies are applied in clinical practice. However, it is not easy to compare these therapies directly.

In this NMA, we primarily concentrated on comparing the efficacy and safety of TACE combined with MTAs. The results manifested that Apat+TACE had the best OS outcomes; Lenv+TACE and Sora+TACE placed second and third, respectively. The first three treatment strategies related to higher PFS outcomes were Lenv+TACE, Apat+TACE, and Oran+TACE. The first three treatment strategies related to higher ORR were Apat+TACE, Sora+TACE, and Lenv+TACE, while DCR was ranked similarly. In addition, there was no statistically significant difference among all treatment regimens with respect to the incidence of AEs and ≥G3-AEs. As a result, it can conclude that Apat+TACE was related to the best OS, ORR, and DCR, whereas Lenv+TACE was linked with the greatest PFS, with no extra AEs or ≥G3-AEs.

Apat, as an anti-angiogenic drug, preferentially inhibits VEGFR-2 tyrosine kinase, as well as slightly inhibits c-kit, c-src and, RET tyrosine kinases (56). It selectively binds to the intracellular ATP binding domain, inhibiting vascular endothelial cell proliferation and migration, reducing tumor angiogenesis, and inhibiting tumor formation (57). Furthermore, it can reverse the multidrug resistance caused by ABC protein and enhance the effectiveness of conventional anticancer drugs (58, 59). By inducing traditional chemotherapy medications and stimulating cell apoptosis, it can also have an anticancer effect (57). The above characteristics of apatinib are highly compatible with TACE treatment, which may be the important reason why Apat+TACE can stand out in many combined therapies.

For a long time, the comparison of survival time of HCC patients between Sora+TACE and Apat+TACE has been controversial. Qiu et al. (54) found that the PFS of the Apat+TACE group was shorter than that of the Sora+TACE group, while the OS of the two groups was not significantly different. Besides, Cao et al. (53) argued that in a retrospective study, the prognosis for both treatments was equivalent in patients with portal vein tumor thrombosis. It is worth mentioning that Apatinib has a tenfold higher affinity for VEGFR-2 tyrosine kinase

A

TACE	1.05 (0.3, 3.64)	1.45 (0.61, 3.44)	1.56 (0.89, 2.84)	1.61 (0.71, 3.65)	2.46 (0.55, 11.33)
0.95 (0.27, 3.28)	**sorafenib+TACE**	1.37 (0.56, 3.34)	1.49 (0.38, 5.83)	1.53 (0.35, 6.68)	2.34 (0.99, 5.63)
0.69 (0.29, 1.65)	0.73 (0.3, 1.78)	**lenvatinib+TACE**	1.08 (0.39, 3.09)	1.11 (0.34, 3.62)	1.7 (0.49, 6.01)
0.64 (0.35, 1.12)	0.67 (0.17, 2.63)	0.93 (0.32, 2.59)	**orantinib+TACE**	1.03 (0.38, 2.78)	1.57 (0.31, 7.99)
0.62 (0.27, 1.4)	0.65 (0.15, 2.84)	0.9 (0.28, 2.92)	0.97 (0.36, 2.66)	**brivanib+TACE**	1.53 (0.28, 8.43)
0.41 (0.09, 1.82)	0.43 (0.18, 1.01)	0.59 (0.17, 2.04)	0.64 (0.13, 3.23)	0.65 (0.12, 3.56)	**apatinib+TACE**

B

TACE	1.02 (0.55, 1.9)	1.04 (0.56, 1.94)	1.65 (0.88, 3.09)	1.71 (0.7, 4.16)
0.98 (0.53, 1.82)	**orantinib+TACE**	1.02 (0.43, 2.43)	1.62 (0.67, 3.92)	1.68 (0.57, 4.97)
0.96 (0.51, 1.79)	0.98 (0.41, 2.35)	**brivanib+TACE**	1.59 (0.65, 3.82)	1.64 (0.55, 4.84)
0.61 (0.32, 1.14)	0.62 (0.25, 1.5)	0.63 (0.26, 1.53)	**sorafenib+TACE**	1.03 (0.55, 1.93)
0.59 (0.24, 1.43)	0.6 (0.2, 1.77)	0.61 (0.21, 1.81)	0.97 (0.52, 1.81)	**lenvatinib+TACE**

FIGURE 5
Pooled safety indicators estimates of network meta-analysis. **(A)** Pooled odds ratios (95% confidence intervals) of ≥Grade-3 adverse events. **(B)** Pooled odds ratios (95% confidence intervals) of adverse events.

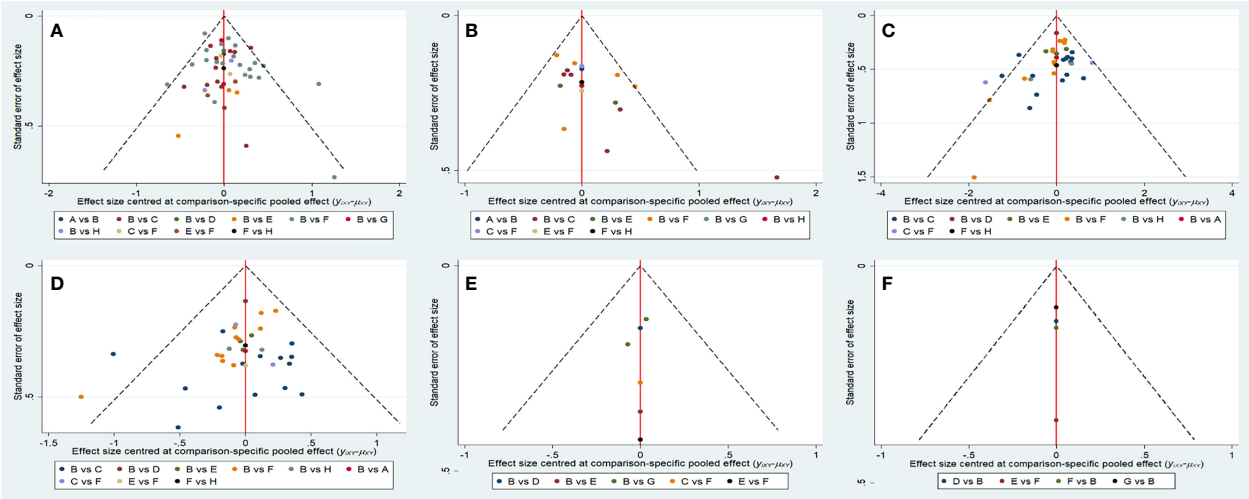

FIGURE 6
Funnel plots of each evaluation index. **(A)** Overall survival. **(B)** Progression-free survival. **(C)** Objective response rate. **(D)** Disease control rate. **(F)** ≥Grade-3 adverse events. **(E)** Adverse events. A, anlotinib+TACE; B, TACE; C, apatinib+TACE; D, brivanib+TACE; E, lenvatinib+TACE; F, sorafenib +TACE; G, orantinib+TACE; H, sunitinib+TACE.

than sorafenib (60). In our NMA, the OS and PFS of Apat+TACE were significantly better than those of Sora+TACE.

Regarding ORR, Apat+TACE had a higher ORR, suggesting a more significant proportion of patients with a 30% tumor decrease and maintenance for more than 4 weeks after Apat+TACE treatment. Because doctors or patients can clearly see the comparison of tumor bodies before and after therapy from the imaging, this sign is more intuitive for effect after treatment. However, ORR has a disadvantage in that it can only assess the efficacy of individual treatments and cannot reflect the overall advantages of the patient's whole course of therapy. Apat+TACE fared better in terms of DCR, suggesting that it helped increase patient compliance and provided opportunities for more follow-up treatment in the future.

Hand-foot syndrome, hypertension, fatigue, and diarrhea were some of the most frequent adverse reactions to using TACE combined with MTAs. Compared to other combination therapy, Sora+TACE had more significant instances of erythema multiforme, rash, liver dysfunction, and alopecia. Thrombocytopenia and neutropenia were the side effects of Suni+TACE that occurred more frequently than those of other combination therapies. Pyrexia was the side effect that occurred more frequently with Oran+TACE than with other combination therapies. Liu et al. (43) reported in their study that two patients in the Apat+TACE group had to stop the trial for antihypertensive treatment due to severe hypertension but could continue the trial after treatment. Lu et al. (15) found that patients with severe hand-foot syndrome need to stop taking medication for two weeks and resume treatment after symptoms subside. Two other patients withdrew from treatment due to severe hand-foot syndrome. Lencioni et al. (13) reported that 4 deaths in the Sora+TACE group might be related to Sora. Zhu et al. (32) reported that patients with ≥G3-AEs in the Sora+TACE group needed to reduce the dosage of Sora or interrupt treatment. In their study, Kudo et al. (14) reported a case of death within 30 days after receiving Sora+TACE treatment. Chen et al. (36) reported in their study that 6 patients were forced to stop taking Lenv+TACE due to uncontrolled hypertension. However, in other studies, adverse reactions can be controlled by reducing drug dosage or providing symptomatic therapy without the occurrence of drug-related deaths. Therefore, it can be considered that combination therapy is within an acceptable range and is tolerable. In our NMA, there was no statistically significant difference in the incidence of AEs and ≥G3-AEs among various treatment strategies.

In our NMA, the OS, ORR, and DCR of Apat+TACE were better than that of Lenv+TACE apart from PFS, but there was no statistical difference between them. Similarly, Zhang et al. (61) compared the efficacy of TACE combined with four different tyrosine kinase inhibitors (TKIs) in their study. They deemed that the OS, PFS, ORR, and DCR of Lenv+TACE were better than those of Apat+TACE, but the difference was not statistically significant. We considered the reasons as follows: First, for OS and PFS indicators, since most of them are extracted from the Kaplan-Meier curve, different extractors had different subjective feelings, resulting in different extracted data. Second, we did not include those studies that had received systemic HCC treatment before the experiment or received other therapies at the same time during the experiment, which was different from the study of Zhang et al. (61). As a result, it is necessary to carry out a sizeable multi-center RCT to compare the efficacy between Apat+TACE and Lenv+TACE.

As an oral multikinase inhibitor, Sora directly suppresses tumor growth by regulating RAF/MEK/ERK pathway (62). It can also indirectly inhibit tumor growth and proliferation by inhibiting VEGFR and PDGFR to inhibit tumor neovascularization (63). There are already many meta-analyses comparing Sora+TACE with TACE. Zhang et al. (64) reported that Sora+TACE significantly outperformed TACE in terms of 1-year OS, 2 years OS, 3 years OS, 5 years OS, ORR, and DCR. Patients tolerated combination treatment well, despite the possibility of side effects

related to Sora. Li et al. (65) mainly focused on the efficacy comparison between Sora+TACE and TACE. They thought that OS and time to progression (TTP) of combined treatment were significantly better than monotherapy. Chen et al. (66) believed that compared to the monotherapy group, the combined treatment group showed a significant increase in OS, TTP, and ORR. Also, there was no statistically significant difference in the incidence of AEs between the two treatment groups.

In our NMA, the Apat+TACE group had significantly better OS, PFS, ORR, and DCR than the TACE group, while there was no statistically significant difference in AEs and ≥G3-AEs between the two groups. Many meta-analyses currently exist comparing Apat+TACE with TACE. Wei et al. (67) indicated that compared with the TACE group, the Apat+TACE group had significant benefits in 6 months OS, 1 year OS, and 2 years OS. Exception for the incidence of hand-foot syndrome, proteinuria, hypertension, and diarrhea, the Apat+TACE group was significantly higher than the TACE group. There was no statistical difference in the incidence of other adverse reactions. At the same time, Gong et al. (68) also concluded similarly to the foregoing.

Lenv, as an oral multi-kinase inhibitor, inhibits VEGFR-1/2/3, fibroblast growth factor receptor (FGFR) 1-4, and PDGFR-α, RET, and KIT targets, thereby inhibiting tumor cell growth and tumor angiogenesis (69). Liu et al. (70) conducted a meta-analysis comparing Lenv+TACE with Sora+TACE and found that the OS and PFS of the Lenv+TACE group were significantly better than those of Sora+TACE. In terms of safety, the incidence of hypertension and proteinuria was significantly higher in the Lenv+TACE group than in the Sora+TACE group, while the opposite was true for the hand-foot syndrome. The PFS of the Lenv+TACE group was significantly better than that of the Sora +TACE group in our NMA. In terms of OS, AEs, and ≥G3-AEs, there was no statistically significant difference between the two groups. As a result, there is disagreement on the efficacy of the comparison between Lenv+TACE and Sora+TACE, and a large, multicenter RCT is required to validate it.

Suni, as a tyrosine kinase inhibitor (TKI), targets PDGF-α/β, VEGFR-1/2/3, KIT, FLT-3, CSF-1, and RET. Briv, as a TKI, selectively inhibits VEGFR and FGFR. Anlo, as a TKI, targets VEGFR, FGFR, PDGFR, and c-kit (71). Oran, as a TKI, targets VEGFR-2 and PDGFR-β. Through the above mechanisms, it exerts its anti-tumor proliferation and anti-tumor angiogenesis effects (72). Due to the limited number of studies on the combination of the three MTAs combined with TACE for the treatment of HCC, there is no meta-analysis on the combination of the MTAs and TACE for the treatment of HCC.

Our NMA had the following advantages. Firstly, studies that used other systemic therapies before or during MTAs+TACE therapy or TACE monotherapy were excluded to reflect the efficacy of MTAs+TACE more accurately. Secondly, it summarized the current research on MTAs combined with TACE to compare the efficacy and safety of various MTAs+TACE.

At the same time, however, there were also some limitations in the NMA. Firstly, among the 45 studies we included, only 5 were related to the comparison between MTAs and TACE, while the rest was compared between MTAs+TACE and TACE. Therefore, merging and comparing the comparisons of MTAs+TACE may undermine the credibility of the research. Secondly, since the HR and 95% CIs of the OS and PFS were rarely directly provided by the original study, we needed to extract data from the curve. Due to the subjective nature of extracting data, the accuracy of HR and its CIs related to OS and PFS may be affected. Thirdly, out of the 45 studies we included, only 10 were RCTs, which may bring confounding factors to our research and lead to the risk of selective bias.

The network meta-analysis showed that apatinib+TACE displayed the best OS, ORR, and DCR with no additional AEs and ≥G3-AEs. Therefore, for the treatment scheme of MTAs combined with TACE, apatinib+TACE may be the most effective treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

JL was responsible for writing the manuscript. BC and ZL analyzed the data. BC was responsible for research and design. JL, BC, and ZL searched the literature together. BC participated in the revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1179431/full#supplementary-material

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Adjuvant TACE may not improve recurrence-free or overall survival in HCC patients with low risk of recurrence after hepatectomy

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Background: To identify whether adjuvant transarterial chemoembolization (TACE) can improve prognosis in HCC patients with a low risk of recurrence (tumor size ≤ 5 cm, single nodule, no satellites, and no microvascular or macrovascular invasions) after hepatectomy.

Methods: The data of 489 HCC patients with a low risk of recurrence after hepatectomy from Shanghai Cancer Center (SHCC) and Eastern Hepatobiliary Surgery Hospital (EHBH) were retrospectively reviewed. Recurrence-free survival (RFS) and overall survival (OS) were analyzed with Kaplan-Meier curves and Cox proportional hazards regression models. The effects of selection bias and confounding factors were balanced using propensity score matching (PSM).

Results: In the SHCC cohort, 40 patients (19.9%, 40/201) received adjuvant TACE, and in the EHBH cohort, 113 patients (46.2%, 133/288) received adjuvant TACE. Compared to the patients without adjuvant TACE after hepatectomy, patients receiving adjuvant TACE had significantly shorter RFS (P=0.022; P=0.014) in both cohorts before PSM. However, no significant difference existed in OS (P=0.568; P=0.082). Multivariate analysis revealed that serum alkaline phosphatase and adjuvant TACE were independent prognostic factors for recurrence in both cohorts. Furthermore, significant differences existed in tumor size between the adjuvant TACE and non-adjuvant TACE groups in the SHCC cohort. There were differences in transfusion, Barcelona Clinic Liver Cancer stage and tumor-node-metastasis stage in the EHBH cohort. These factors were balanced by PSM. After PSM, patients with adjuvant TACE after hepatectomy still had significantly shorter RFS than those without (P=0.035; P=0.035) in both cohorts, but there was no difference in OS (P=0.638; P=0.159).

Adjuvant TACE was the only independent prognostic factor for recurrence in multivariate analysis, with hazard ratios of 1.95 and 1.57.

Conclusions: Adjuvant TACE may not improve long-term survival and might promote postoperative recurrence in HCC patients with a low risk of recurrence after hepatectomy.

KEYWORDS

hepatocellular carcinoma, hepatectomy, postoperative adjuvant TACE, low risk of recurrence, prognosis

Introduction

Recurrence after resection is the main obstacle for hepatocellular carcinoma (HCC) patients and limits surgical efficacy (1, 2). Many adjunctive therapies have been used to reduce the risk of recurrence and metastasis after liver resection (3–5).

Transarterial chemoembolization (TACE) has been the most widely used treatment for intermediate-stage HCC and preoperative downstaging treatment (2, 6–8). Preventively, adjuvant TACE has been used to reduce the risk of recurrence and prolong survival for HCC patients after hepatectomy (9). And it is usually performed approximately 4 weeks after hepatectomy.

However, it remains controversial whether adjuvant TACE can benefit HCC patients after hepatectomy (10, 11). A growing amount of supporting evidence has confirmed that, for the high-risk recurrence population (tumor size > 5 cm, multiple nodules, circulating tumor cells, microvascular invasion (MVI) and macrovascular invasion), adjuvant TACE can significantly reduce the recurrence rate and prolong long-term survival (5, 12–18). The procedure might improve the prognosis by eliminating residual cancer cells. Interestingly, for HCC patients with a low risk of recurrence (tumor size ≤ 5 cm, single nodule, MVI-negative and no macrovascular invasions), it is unclear whether adjuvant TACE could provide benefits after hepatectomy.

Here, focusing on HCC patients with a low risk of recurrence, we reassessed whether adjuvant TACE could benefit prognosis in these patients after hepatectomy with a propensity score matching (PSM) analysis from two independent cancer centers.

Materials and methods

Patients diagnosed with HCC who underwent hepatectomy between March 2015 and September 2019 at Shanghai Cancer Center (SHCC) in Shanghai, China, and patients diagnosed between December 2009 and June 2010 who underwent hepatectomy at the Eastern Hepatobiliary Surgery Hospital (EHBH) in Shanghai, China, were retrospectively reviewed.

The inclusion criteria were as follows: (1) HCC was diagnosed pathologically after hepatectomy; (2) single nodule; (3) diameter ≤ 5 cm; (4) Child–Pugh A or B liver function; and (5) adjuvant TACE adopted within 2 months after hepatectomy. The exclusion criteria were as follows: (1) recurrent HCC; (2) patients with microvascular or macrovascular invasions or satellites; (3) patients with extrahepatic metastasis; (4) a previous history of treatment of malignancy; (5) recurrence before or at adjuvant TACE; (6) perioperative mortality; and (6) incomplete data.

Data were extracted from medical records, cross-checked and statistically analyzed. The following clinicopathological parameters were extracted and analyzed statistically: sex, age, chronic hepatitis B/C virus (HBV/HCV) infection, transfusion, albumin (ALB), total bilirubin (TBIL), alanine transaminase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), prothrombin time (PT), platelet count, tumor size, differentiation of tumor cells and liver cirrhosis.

The chemotherapeutic regimens used in adjuvant TACE included hydroxycamptothecin, pirarubicin (THP) and floxuridine (FUDR) in the SHCC cohorts and doxorubicin hydrochloride, TPH and epirubicin in the EHBH cohorts. The dosages of these chemotherapeutic drugs and lipiodol were determined by body surface area and liver function.

This study was approved by the Clinical Research Ethics Committee of EHBH and the Institutional Review Board and the Ethics Committee of SHCC. Written informed consent was obtained from all subjects before the operation and (or) TACE. The consent was also obtained for participation in our study.

Follow-up

Patients were followed up as in our previous report (19, 20). Recurrence and overall survival (OS) were used as endpoints. Recurrence-free survival (RFS) was calculated from the date of operation to the date when recurrence or metastasis was diagnosed. OS duration was defined as the interval between surgery and the time of death due to any cause. The most recent EHBH patient has been followed up for five years. The deadline for follow-up in SHCC patients was 03-31-2022. During the follow-up period, patients with recurrence or metastasis were treated with optimal therapeutic methods.

Statistical analysis

MedCalc statistical software (version 19.3, Ostend, West-Vlaanderen, Belgium) was used to analyze the data acquired from this study (21). Continuous variables were analyzed with Student's t

test or the Mann–Whitney U test, and categorical variables were compared with the chi-squared test, Fisher's exact test or Wilcoxon's signed-rank test, where appropriate. Kaplan–Meier curves, log-rank tests and Cox proportional hazards regression analysis were used to analyze recurrence and survival. The effects of selection bias and confounding factors were balanced using PSM (nearest neighbor matching) with the *MatchIt* package in R software (version 4.1.2) (22). All statistical tests were two-tailed, and the difference was considered statistically significant when the *P* value was less than 0.05.

Results

Clinicopathological features of the adjuvant TACE and non-adjuvant TACE cohorts

Overall, 201 HCC patients from SHCC and 288 patients from EHBH were included in our study (Supplementary Figure 1). In the SHCC cohorts, 40 (19.9%, 40/201) patients received TACE after hepatectomy. Correspondingly, 113 (46.2%, 133/288) patients received it in the EHBH cohorts. Except for tumor size, there were no significant differences in clinicopathological parameters between adjuvant TACE and non-adjuvant TACE cohorts in the SHCC cohorts (Table 1). And, there were differences in transfusion, Barcelona Clinic Liver Cancer (BCLC) stage and tumor-node-metastasis (TNM, American Joint Committee on Cancer (AJCC), 8th) stage between adjuvant TACE and non-adjuvant TACE cohorts in the EHBH cohorts (Table 2). These factors were balanced by PSM with nearest neighbor matching. After PSM with 1:2 ratio matching in the SHCC cohort and 1:1 ratio matching in the EHBH cohort, the clinicopathological differences were well balanced between the adjuvant TACE and non-adjuvant TACE groups in both the SHCC and EHBH cohorts (Tables 1, 2). Histograms of propensity scores before and after matching in the two cohorts are shown in Supplementary Figures 2, 3.

TABLE 1 Clinicopathological features of hepatocellular carcinoma patients with low risk of recurrence after liver resection (Shanghai Cancer Center Cohorts).

Clinicopathological features	Adjuvant TACE (n=40)	Non-adjuvant TACE before a PSM (n=161)	Non-adjuvant TACE after a PSM 1:2 (n=80)	P_1 values	P_2 values
Sex, female/male	8/32 (20.0%/80.0%)	20/141 (12.4%/87.6%)	8/72 (10.0%/90.0%)	0.215	0.129
Age, range (years)	55.7±10.8 (35.0-81.0)	56.8±11.0 (31.0-84.0)	57.1±11.4 (31.0-84.0)	0.567	0.524
Hepatitis, Yes/No	29/11 (72.5%/27.5%)	126/35 (78.3%/21.7%)	60/20 (75.0%/25.0%)	0.438	0.768
TBIL, (μmol/L)	12.5 (8.9-18.3)	11.7 (9.1-15.8)	11.3 (8.6-15.1)	0.245	0.126
ALB, range (g/L)	43.4±3.9 (33.3-50.9)	44.2±3.5 (35.6-53.8)	43.7±3.5 (35.6-52.2)	0.194	0.605
ALT, range (U/L)	29.9 (17.9-41.1)	26.0 (18.6-26.0)	23.4 (17.4-40.3)	0.486	0.535
AST, range (U/L)	25.3 (19.4-34.8)	24.0 (19.1-30.6)	24.2 (19.1-33.3)	0.528	0.720
ALP, range (U/L)	75.7 (64.2-89.7)	74.7 (61.9-91.4)	73.5 (62.0-88.1)	0.829	0.574
GGT, range (U/L)	45.5 (26.3-65.5)	35.0 (21.0-58.5)	34.0 (21.0-61.3)	0.166	0.207
AFP, range (ng/mL)	11.0 (4.2-219.3)	6.9 (3.0-109.6)	6.9 (6.9-255.7)	0.163	0.333
CA19-9, range(U/mL)	13.4 (8.3-26.9)	13.8 (8.5-26.0)	13.6 (8.2-26.8)	0.967	0.841
PT, range (second)	13.4 (13.1-14.0)	13.3 (12.9-13.9)	13.2 (12.8-13.7)	0.327	0.137
PLT, range (10^9/L)	164.5 (130.0-213.0)	154.0 (123.5-204.0)	163.0 (129.0-216.8)	0.708	0.427
Transfusion, Yes/No	1/39 (2.5%/97.5%)	5/156 (3.1%/96.9%)	4/76 (5.0%/95.0%)	1.000	0.518
Diameter, range (cm)	3.5 (2.0-4.5)	2.8 (2.0-3.8)	3.1 (2.0-4.2)	0.035	0.714
Intact capsule, Yes/No	18/22 (45.0%/55.0%)	66/95 (41.0%/59.0%)	34/46 (42.5%/57.5%)	0.646	0.794
Differentiation, I/II+III/IV*	4/29/7 (10.0%/72.5%/17.5%)	23/119/19 (14.3%/73.9%/11.8%)	9/61/10 (11.2%/76.3%/12.5%)	0.542	0.519
Liver cirrhosis, Yes/No	28/12 (70.0%/30.0%)	96/65 (59.6%/40.4%)	49/31 (61.3%/38.8%)	0.227	0.346
BCLC Stage, 0/A	12/28 (30.0%/70.0%)	52/109 (32.3%/67.7%)	21/59(26.3%/73.8%)	0.780	0.665
Chinese Stage, Ia	40 (100.0.%)	161 (100.0.%)	80 (100.0.%)	–	–
TNM stage (AJCC, 8th), T1a/T1b	12/28 (30.0%/70.0%)	52/109 (32.3%/67.7%)	21/59(26.3%/73.8%)	0.780	0.665

"*" Classification of Edmondson-Steiner; TACE, transarterial chemoembolization; PSM, propensity score matching; TBIL, total bilirubin; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; AFP, alpha fetal protein; CA19-9, Carbohydrate antigen19-9; PT, prothrombin time; PLT, platelets. P_1 values, adjuvant TACE VS non-adjuvant TACE before a PSM; P_2 values, adjuvant TACE VS non-adjuvant TACE after a PSM; BCLC stage, Barcelona Clinic Liver Cancer stage; TNM stage, tumor node metastasis staging system; AJCC, American Joint Committee on Cancer.

TABLE 2 Clinicopathological features of hepatocellular carcinoma patients with low risk of recurrence after liver resection (Eastern Hepatobiliary Surgery Hospital Cohorts).

Clinicopathological features	Adjuvant TACE (n=113)	Non-adjuvant TACE (n=175)	Non-adjuvant TACE after a PSM 1:1 (n=113)	P_1 values	P_2 values
Sex, female/male	15/98 (13.3%/86.7%)	28/147 (16.0%/84.0%)	17/96 (15.0%/85.0%)	0.526	0.703
Age, range (years)	52.0±9.3 (28.0-76.0)	53.0±11.1 (22.0-83.0)	53.4±11.1 (22.0-83.0)	0.409	0.299
Hepatitis, Yes/No	107/6 (94.7%/5.3%)	164/11 (93.7%/6.3%)	105/8 (92.9%/7.1%)	0.731	0.581
TBIL, (μmol/L)	13.4 (10.1-17.6)	14.3 (11.2-17.1)	13.3 (10.8-16.7)	0.561	0.143
ALB, range (g/L)	42.5±4.2 (29.4-53.4)	42.5±4.0 (31.4-51.7)	42.4±4.0 (31.4-51.5)	0.923	0.988
ALT, range (U/L)	35.4 (27.3-60.5)	33.1 (24.0-47.0)	35.8 (24.3-48.4)	0.060	0.201
AST, range (U/L)	31.8 (23.7-43.3)	29.0 (23.5-38.8)	29.0 (23.9-38.7)	0.175	0.221
ALP, range (U/L)	74.0 (61.5-89.5)	76.0 (61.0-89.0)	76.0 (61.0-86.5)	0.732	0.826
GGT, range (U/L)	47.0 (33.0-80.5)	41.0 (28.0-69.0)	41.0 (28.0-69.0)	0.117	0.137
AFP, range (ng/mL)	30.4 (5.8-262.6)	15.5 (4.8-324.3)	16.4 (4.8-388.0)	0.532	0.744
CA19-9, range(U/mL)	20.2 (11.9-32.6)	20.0 (10.4-32.3)	20.4 (10.5-32.9)	0.317	0.603
PT, range (second)	12.0 (11.6-13.1)	12.0 (11.5-12.7)	12 (11.5-12.5)	0.416	0.110
PLT, range (10^9/L)	143 (100.5-181.0)	133.0 (99.0-179.0)	139.0 (96.5-178.0)	0.501	0.450
Transfusion, Yes/No	8/105 (7.1%/92.9%)	28/147 (16.0%/84.0%)	8/105 (7.1%/92.9%)	0.025	1.000
Diameter, range (cm)	3.1 (2.5-4.0)	3.0 (2.1-4.0)	3.0 (2.5-4.0)	0.380	0.393
Intact capsule, Yes/No	60/53 (53.1%/46.9%)	76/99 (43.4%/56.6%)	68/45 (60.2%/39.8%)	0.563	0.283
Differentiation, I/II+III/IV*	11/71/31 (9.3%/62.8%/27.4%)	19/112/44 (10.9%/64.0%/25.1%)	14/64/35 (12.4%/56.6%/31.0%)	0.889	0.617
Liver cirrhosis, Yes/No	77/36 (68.1%/31.9%)	117/58 (66.9%/33.1%)	68/45 (60.2%/39.8%)	0.820	0.212
BCLC Stage, 0/A	11/102 (9.7%/90.3%)	36/139 (20.6%/79.4%)	8/105 (7.1%/92.9%)	0.015	0.472
Chinese Stage, Ia	113 (100.0.%)	175 (100.0.%)	113 (100.0.%)	-	-
TNM stage (AJCC, 8th), T1a/T1b	11/102 (9.7%/90.3%)	36/139 (20.6%/79.4%)	8/105 (7.1%/92.9%)	0.015	0.472

"*" Classification of Edmondson-Steiner; TACE, transarterial chemoembolization; PSM, Propensity Score Matching; TBIL, total bilirubin; ALB, albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; AFP, alpha fetal protein; CA19-9, Carbohydrate antigen19-9; PT, prothrombin time; PLT, platelets. P_1 values, adjuvant TACE VS non-adjuvant TACE before a PSM; P_2 values, adjuvant TACE VS non-adjuvant TACE after a PSM; BCLC stage, Barcelona Clinic Liver Cancer stage; TNM stage, tumor node metastasis staging system; AJCC, American Joint Committee on Cancer.

Recurrence and OS in the SHCC cohorts and EHBH cohorts

The median follow-up duration of the SHCC cohort was 53.2 ± 2.3 months; the adjuvant TACE group was 53.4 ± 2.6 months and the non-adjuvant TACE groups was 51.1 ± 4.1 months. Intrahepatic recurrence occurred in 62 (30.8%, 62/201) patients, extrahepatic metastases occurred in 7 (3.5%, 7/201) patients, and death occurred in 19 (9.5%, 19/201) patients. The 1-, 3- and 5-year recurrence rates were 8.5%, 26.9% and 35.1%, respectively. The 1-, 3- and 5-year survival rates were 99.5%, 95.9% and 84.9%, respectively.

In the EHBH cohorts, the median follow-up was more than 60 months and the adjuvant TACE and non-adjuvant TACE groups were also more than 60 months. Intrahepatic recurrence occurred in 109 (37.8%, 109/288) patients, extrahepatic metastases occurred in 9 (3.1%, 9/288) patients, and death occurred in 25 (8.7%, 25/288) patients. The 1-, 3- and 5-year recurrence rates were 10.1%, 25.3% and 39.0%, respectively. The 1-, 3- and 5-year survival rates were 98.6%, 94.7% and 91.1%, respectively.

Prognostic factors of recurrence and OS in SHCC cohorts

The results of univariate analysis for recurrence and OS in the SHCC cohorts before PSM are shown in Supplementary Table 1 (Figure 1). The mean RFS was 51.0±4.8 months in the adjuvant TACE group, with 1-, 3-, and 5-year recurrence rates of 10.0%, 44.1% and 48.7%, respectively, and RFS was 66.0±2.4 months, with 1-, 3-, and 5-year recurrence rates of 8.1%, 22.6% and 31.9%, respectively, in the non-adjuvant TACE group. Kaplan–Meier curves showed that patients treated with adjuvant TACE had higher recurrence rates and shorter RFS after hepatectomy (Figure 1A, P=0.022). However, no significant difference was

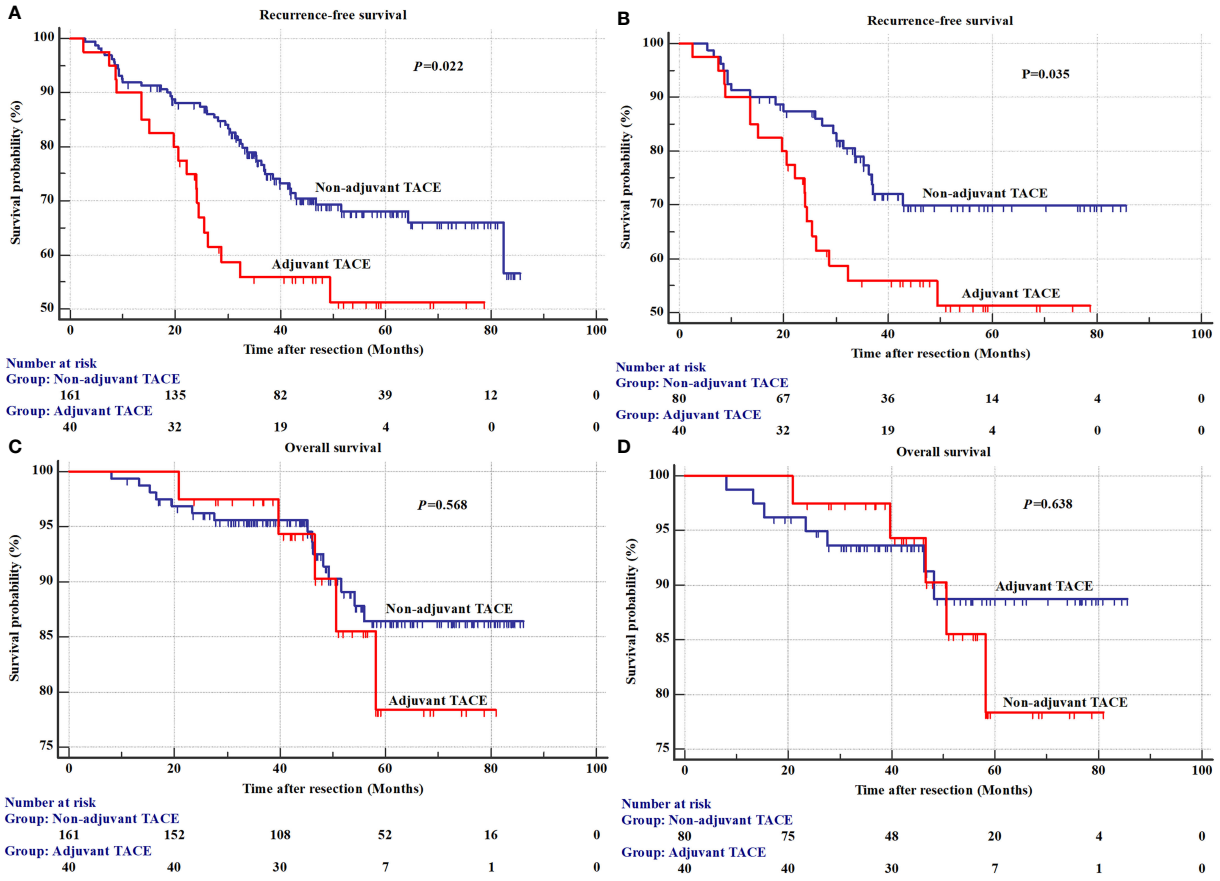

FIGURE 1
The recurrence and overall survival between adjuvant TACE and non-adjuvant TACE after hepatectomy in Shanghai Cancer Center cohorts. **(A)** Recurrence before a propensity score matching analysis; **(B)** Overall survival before a propensity score matching analysis; **(C)** Recurrence after a propensity score matching analysis; **(D)** Overall survival after a propensity score matching analysis. TACE, transarterial chemoembolization.

found in OS between adjuvant TACE and non-adjuvant TACE patients (Figure 1C, *P*=0.568). Cox proportional hazards multivariate analysis revealed that adjuvant TACE and serum ALP were independent prognostic factors for recurrence (Table 3). After PSM, the Kaplan–Meier curves still showed that patients with adjuvant TACE had higher recurrence rates and shorter RFS after hepatectomy. No significant difference existed in OS between these two groups (Figure 1B, *P*=0.035; Figure 1D, *P*=0.638).

TABLE 3 Multivariate analysis of clinicopathological parameters associated with recurrence for hepatocellular carcinoma patients with low risk of recurrence after liver resection.

Clinicopathological parameters	HR	95% CI	*P* values
Before a PSM (SHCC Cohorts)			
Alkaline phosphatase, (U/L)	1.01	1.003-1.023	0.011
Adjuvant TACE, Yes/No	1.86	1.076-3.222	0.026
After a PSM (SHCC Cohorts)			
Adjuvant TACE, Yes/No	1.95	1.038-3.663	0.038
Before a PSM (EHBH Cohorts)			
Alkaline phosphatase, (U/L)	1.01	1.001-1.013	0.023
Adjuvant TACE, Yes/No	1.62	1.113-2.356	0.012
After a PSM (EHBH Cohorts)			
Adjuvant TACE, Yes/No	1.57	1.029-2.383	0.036

HR, hazard ratios; CI, confidence interval; PSM, propensity score matching; SHCC, Shanghai Caner Center; TACE, transarterial chemoembolization; EHBH, Eastern Hepatobiliary Surgery Hospital.

Adjuvant TACE was the only independent prognostic factor for recurrence, with a hazard ratio (HR) of 1.95 (Table 3, 95% confidence interval (CI): 1.04-3.66, *P*=0.038) by multivariate analysis (Supplementary Table 2; Table 3).

Prognostic factors of recurrence and OS in EHBH cohorts

The results of univariate analysis for recurrence and OS in the EHBH cohorts before PSM are shown in Supplementary Table 3. The mean RFS was 43.6±2.0 months in the adjuvant TACE group, with 1-, 3-, and 5-year recurrence rates of 14.2%, 32.1% and 47.3%, respectively, and RFS was 49.3±1.4 months, with 1-, 3-, and 5-year recurrence rates of 7.4%, 22.1% and 33.5%, respectively, in the non-adjuvant TACE group. Kaplan–Meier curves also showed a significant difference in recurrence but not in OS between adjuvant TACE and non-adjuvant TACE patients after hepatectomy (Figure 2A, *P*=0.014; Figure 2C, *P*=0.082). Cox proportional hazards multivariate analysis also revealed that adjuvant TACE and serum ALP were both independent prognostic factors for recurrence (Table 3). Similarly, adjuvant TACE remained the only independent prognostic factor for recurrence, with an HR of 1.57 (Table 3, 95% CI: 1.03-2.38, *P*=0.036) by multivariate analysis after PSM (Figures 2B, D; Table 3; Supplementary Table 4).

Discussion

Postoperative recurrence is the main obstacle to improving surgical efficacy in HCC (23). Increasing supporting evidence has confirmed that adjuvant TACE can benefit the high-risk recurrence population (4, 5, 12–18). However, it remains unclear whether adjuvant TACE can benefit patients with a low risk of recurrence after hepatectomy. In our study, PSM analysis revealed that patients receiving adjuvant TACE had significantly shorter RFS than those who did not, and that adjuvant TACE could not prolong the OS for patients with a low risk of recurrence after hepatectomy.

As early as 2004, Ren reported that in HCC patients with risk factors (tumors with a size greater than 5 cm, multiple nodules, and vascular invasion) for residual tumors after hepatectomy, adjuvant TACE could prolong survival but not in patients without risk factors for residual tumors (9). Since then, clinical studies have begun to pay attention to the relationship between adjuvant TACE

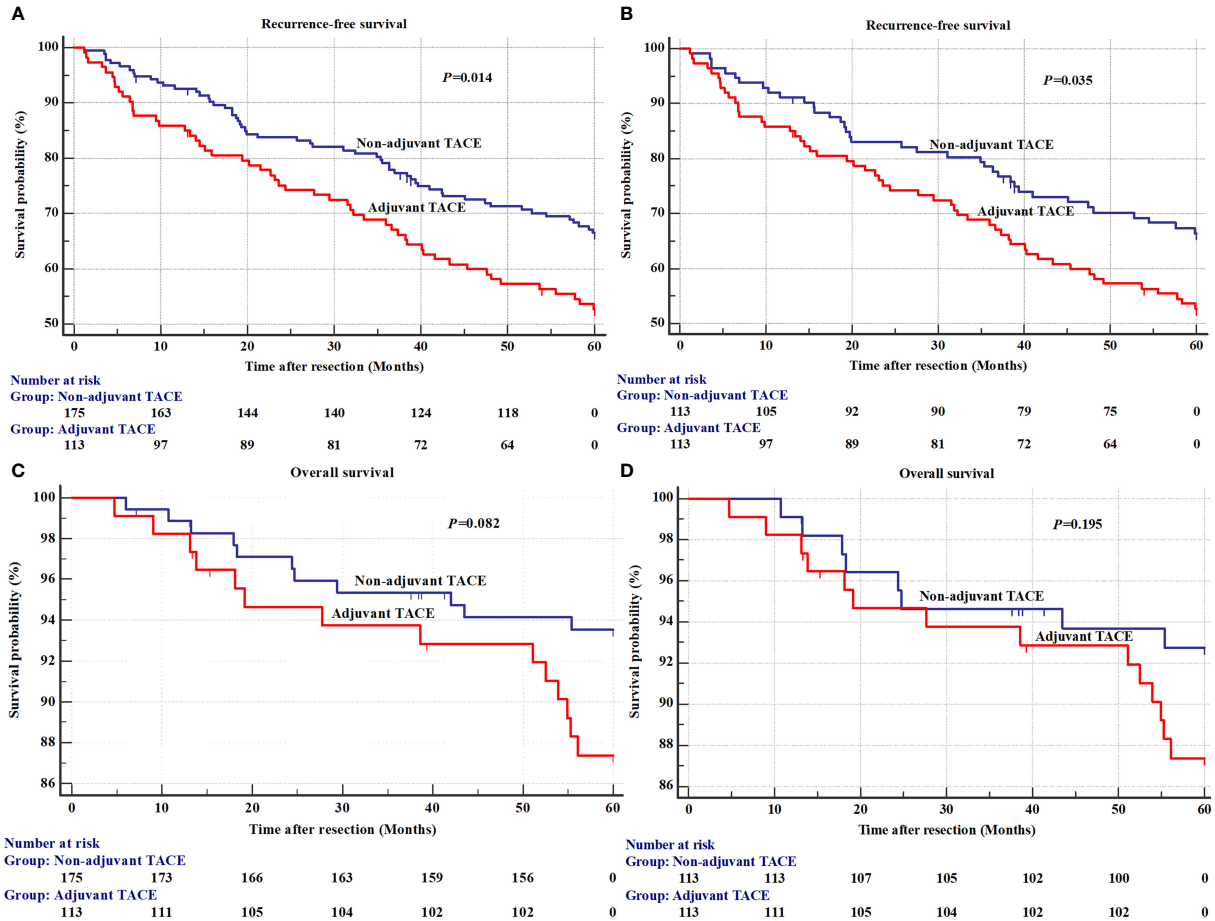

FIGURE 2
The recurrence and overall survival between adjuvant TACE and non-adjuvant TACE after hepatectomy in Eastern Hepatobiliary Surgery Hospital (EHBH) Cohorts. **(A)** Recurrence before a propensity score matching analysis; **(B)** Overall survival before a propensity score matching analysis; **(C)** Recurrence after a propensity score matching analysis; **(D)** Overall survival after a propensity score matching analysis. TACE, transarterial chemoembolization.

and postoperative recurrence risk (13, 24–28). They also reported that adjuvant TACE can significantly reduce recurrence risk and prolong RFS and OS in HBV-related HCC patients with intermediate (a single tumor > 5 cm without MVI) or high risk of recurrence (single tumor with MVI or 2 or 3 tumors). However, patients with a low recurrence risk (single tumor ≤ 5 cm without MVI) were not included (13).

In addition, numerous meta-analyses have performed independent analyses of the risk factors for residual tumors (14, 16, 29–36). Among them, 5 studies performed subgroup analysis on the low risk of recurrence population (30–32, 34, 35). In 2014, Cheng reported that in HCC patients with a tumor size ≤ 5 cm, adjuvant TACE did not benefit disease-free survival (DFS) (30). Qi also found that in patients with small HCC (size ≤ 5 cm) or without vascular invasion, no significant differences existed in DFS and OS between the adjuvant TACE and adjuvant TACE groups (31). However, another study indicated that adjuvant TACE could benefit OS but not RFS in HCC patients with a tumor size < 5 cm (32). In addition, Huo also found that adjuvant TACE can significantly improve 1-year DFS and 5-year OS in HCC patients with a tumor size ≤ 5 cm and prolong 5-year DFS in patients without MVI but with OS (34). In contrast, Chen reported that in HCC patients with a tumor size ≤ 5 cm, a single tumor or MVI negativity, adjuvant TACE could not improve outcomes and could potentially promote recurrence after resection (35). The latest retrospective study also showed that adjuvant TACE might promote postoperative recurrence, especially for HCC patients without MVI, tumor size ≤ 5 cm and preoperative AFP < 400 ng/ml (37).

In our study, patients with a high risk of recurrence, such as those with multiple nodules, macrovascular invasion, microvascular invasion, satellites and larger tumor size (>5 cm), were excluded, and a total of 489 HCC patients (201 from SHCC and 288 from EHBH) were included. All patients had early-stage HCC (BCLC Stage 0 or A, Chinese Stage Ia and TNM Stage TIa or TIb; Tables 1, 2). Comparatively, these patients have a lower risk of recurrence and longer long-term survival after hepatectomy. In the SHCC cohorts, 40 HCC patients (19.9%, 40/201) who received adjuvant TACE after hepatectomy had significantly shorter RFS than patients who did not receive adjuvant TACE (Figure 1A, P=0.022). However, no significant difference existed in OS (Figure 1C, P=0.568). The Cox proportional hazards multivariate analysis indicated that serum ALP and adjuvant TACE were both independent prognostic factors for recurrence (Table 3). After PSM analysis to balance the differences between the adjuvant TACE and non-adjuvant TACE groups, the Kaplan–Meier curves showed a significant difference in RFS, but not in OS, between adjuvant TACE and non-adjuvant TACE patients after hepatectomy (Figure 1B, P=0.035; Figure 1D, P=0.638). Multivariate analysis revealed that adjuvant TACE was the only independent prognostic factor for recurrence (Table 3). Similar results were also acquired in the EHBH cohorts (Figure 2; Table 3). The study also revealed that patients receiving TACE after hepatectomy had significantly shorter RFS before or after PSM, and adjuvant TACE was an independent prognostic factor for recurrence by multivariate analysis. It seems that in the low risk of recurrence population, adjuvant TACE could promote postoperative recurrence after hepatectomy but had no significant effect on OS. This outcome might be caused by liver function injury and immunological function damage induced by TACE (10, 11, 38). Recently, some models for predicting adjuvant TACE benefit in HCC patients have been proposed (39–42). They might constitute effective ways to select the population who can benefit from it.

There are several limitations of our study. First, it was a retrospective study with the inherent defects associated with such studies even after PSM, and a prospective study is required to validate the conclusions. Second, adjuvant TACE after resection usually required a comprehensive decision from the surgeon according to intraoperative and postoperative examinations. Because of selection bias, the recurrence risk of patients receiving adjuvant TACE may be higher than that of patients not receiving adjuvant TACE. Even if they received adjuvant TACE after resection, their outcomes may not be better than the outcomes of those who did not. Third, the cohorts come from two different institutions but were treated during different time periods (SHCC cohorts from March 2015 through September 2019; EHBH cohorts from December 2009 through June 2010). Treatment advances might have affected the prognoses of HCC patients and incurred recurrence and survivorship bias. Fourth, the mechanism for adjuvant TACE promoting postoperative recurrence need exploring.

Conclusion

In summary, we focused on HCC patients with a low risk of recurrence reassessed whether adjuvant TACE could benefit prognosis in these populations and found that adjuvant TACE may not improve long-term survival and might promote postoperative recurrence in HCC patients with a low risk of recurrence after hepatectomy. More clinical trials with higher levels of evidence are needed and could help clinicians perform better interventions for these patients after curative resection.

Data availability statement

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

Ethics statement

This study was approved by the Clinical Research Ethics Committee of Eastern Hepatobiliary Surgery Hospital and Institutional Review Board and the Ethics Committee of Shanghai Cancer Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study concept and design (L-HF, Y-YZ, J-MZ, W-MC, HD, and LW), acquisition of data (J-MZ, MW, W-QX, TZ, and A-RM), analysis and interpretation of data (L-HF, Y-YZ, J-MZ, W-MC, HD, and LW), drafting of the manuscript (L-HF, Y-YZ, and J-MZ), critical revision of

the manuscript for important intellectual content (W-MC, HD, and LW), administrative, technical, or material support (MW, W-QX, TZ, and A-RM), and study supervision (W-MC, HD, and LW). All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

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Development of ensemble learning models for prognosis of hepatocellular carcinoma patients underwent postoperative adjuvant transarterial chemoembolization

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Background: Postoperative adjuvant transarterial chemoembolization (PA-TACE) has been increasing widely used to improve the prognosis of hepatocellular carcinoma (HCC) patients. However, clinical outcomes vary from patient to patient, which calls for individualized prognostic prediction and early management.

Methods: A total of 274 HCC patients who underwent PA-TACE were enrolled in this study. The prediction performance of five machine learning models was compared and the prognostic variables of postoperative outcomes were identified.

Results: Compared with other machine learning models, the risk prediction model based on ensemble learning strategies, including Boosting, Bagging, and Stacking algorithms, presented better prediction performance for overall mortality and HCC recurrence. Moreover, the results showed that the Stacking algorithm had relatively low time consumption, good discriminative ability, and the best prediction performance. In addition, according to time-dependent ROC analysis, the ensemble learning strategies were found to perform well in predicting both OS and RFS for the patients. Our study also found that BCLC Stage, hsCRP/ALB and frequency of PA-TACE were relatively important variables in both overall mortality and recurrence, while MVI contributed more to the recurrence of the patients.

Conclusion: Among the five machine learning models, the ensemble learning strategies, especially the Stacking algorithm, could better predict the prognosis of HCC patients following PA-TACE. Machine learning models could also help clinicians identify the important prognostic factors that are clinically useful in individualized patient monitoring and management.

KEYWORDS

machine learning, hepatocellular carcinoma, postoperative adjuvant TACE, recurrence, prognosis

1 Introduction

Liver cancer is the sixth most prevalent malignancy and the third leading cause of cancer-related death worldwide (1, 2). By 2025, the estimated incidence of liver cancer may exceed 1 million (3). Hepatocellular carcinoma (HCC) is the most common primary liver cancer, accounting for about 75%-85% (4). Although curative hepatectomy is still recommended as the main curative treatment for HCC patients with adequate liver function (5, 6), postoperative prognosis of HCC patients is jeopardized by a high recurrence rate (7). Therefore, several postoperative adjuvant therapies have been developed to reduce the risk of recurrence and improve overall survival (8–10). Transarterial chemoembolization (TACE), which has long been one of the first-line treatments for unresectable HCC (11), is now most widely used as an adjuvant therapy after curative resection for HCC with many recurrence risk factors (12–14). Substantial studies have also shown that postoperative adjuvant TACE (PA-TACE) is beneficial for HCC patients with more tumor numbers, larger tumor size, and microvascular invasion (15–18), especially for those with portal vein tumor thrombus (19). However, few studies have established effective and practical prediction models for prognosis of HCC patients underwent PA-TACE and achieved satisfactory prediction efficacy. Therefore, novel prediction models are needed to facilitate clinical decision making in early management and further improve patient outcomes.

Machine learning, a type of computer science that makes empirical predictions from multi-dimensional datasets, is increasingly being applied to modern medical research, including HCC (20–23). In the prognostic prediction of HCC, it has shown superior advantages in image recognition and feature selection compared with traditional methods, thereby improving the accuracy of the model prediction and subsequent results (21, 22, 24). The rise of artificial intelligence (AI) technology has also brought many new machine learning strategies to predict patient prognosis. In recent researches, several ensemble learning strategies, including Boosting and Bagging algorithm have been developed for HCC and achieved encouraging results (25–27). Different from other machine learning methods that typically apply one model or one algorithm to a specific task, ensemble learning performs greater flexibility in model selection. Specific training strategies could be set for complex clinical datasets to improve the performance of the ensemble learning strategy.

In summary, this study aimed to utilize and compare different machine learning algorithms to establish a better prediction model for survival and recurrence of HCC patients underwent PA-TACE. Five machine learning models, including three novel ensemble learning models and two other models, were selected to provide intelligent postoperative monitoring and management for the patients. We also explored the variable importance and verified important prognostic indicators of postoperative outcomes.

2 Materials and methods

2.1 Patients and study design

The database was retrospectively derived from HCC patients who received curative resection and PA-TACE at Sichuan Provincial People's Hospital between May 2018 and May 2022. The inclusion criteria were included as following: (1) pathological confirmation of HCC; (2) no preoperative therapy for primary HCC; (3) R0 surgical resection of tumor with curative intent; (4) TACE as the only adjuvant treatment; (5) received the first adjuvant TACE within 2 months after resection. Patients who (1) having history of non-HCC malignancies or concurrent with other malignancies; (2) diagnosed with HCC relapse, or distant metastasis; (3) died within 30 days after surgery or lost to follow-up were excluded from this study. The flow chart of the study design can be found in Figure 1.

The study was approved by the Human Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, and written informed consent was obtained from all participants. All procedures were performed in accordance with the ethical guidelines of the Helsinki Declaration.

2.2 Clinical variables and definitions

The clinicopathological characteristics collected from the database included laboratory tests, tumor characteristics, inflammatory-based prognostic indices, and clinical stages. All laboratory tests were collected within 1 week before the operation, including serum indicators, liver and coagulation functions, and hepatitis B virus markers. The tumor characteristics included

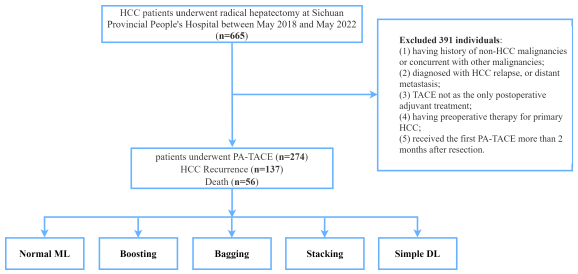

FIGURE 1
The flowchart of patients enrolled in this study. HCC, hepatocellular carcinoma; PA-TACE, postoperative adjuvant transarterial chemoembolization; ML, machine learning; DL, deep learning.

differentiation, cirrhosis, the number of tumors, the diameter of the largest nodule, microvascular invasion and so on. Microvascular invasion (MVI) is defined as the presence of HCC microemboli in blood vessels lined by endothelial cells under histological microscope (28). Nowadays, various inflammatory-based prognostic biomarkers are widely used to predict the prognosis of cancer patient. Our study included neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), high sensitivity C-reactive protein (hsCRP)/albumin (ALB), and prognostic nutritional index (PNI). NLR and PLR were calculated as neutrophil/lymphocyte counts and platelet/lymphocyte counts, respectively (29). SII and SIRI were defined as platelet × neutrophil/lymphocyte counts and monocytes × neutrophil/lymphocyte counts, respectively (29, 30). The calculation formula of PNI was as follow: albumin level (g/L) + 5× total lymphocyte count (10^9/L) (31). The clinical stages included Child-Pugh grade, and Barcelona Clinic Liver Cancer (BCLC) stage.

2.3 Follow up

After the surgery, the follow-up was conducted every 3 months in the first year, and then every 6 months thereafter if there was no recurrence or metastasis. The primary outcome was overall survival (OS), which was defined as the time interval from the surgery to death, or the end of the follow-up (July 2022), whichever came first. And the secondary outcome was recurrence-free survival (RFS), which was defined as the time interval from the surgery to death, recurrence, metastasis, or the end of the follow-up (July 2022), whichever came first.

2.4 Statistical analysis

Continuous variables were expressed as the medians and interquartile ranges (Q1–Q3), and categorical variables were expressed as frequency (%). Time-dependent ROC curves were used to detect the prognostic performance of the Boosting, Bagging, and Stacking model for OS and RFS, respectively. Survival curves were plotted using the Kaplan-Meier method and the differences were compared by log rank test. The learning rate represents the step size of the model iteration, and the number of estimators means the number of base learners (base models). Two-sided $p< 0.05$ was considered statistically significant. All statistical analyses were performed using Python version v3.8.10 and GraphPad Prism version 9.2.0.

2.5 Model development

2.5.1 Normal machine learning

As a commonly used supervised classification algorithm, KNN (K Nearest Neighbors) has a simple structure and good performance. According to different weight calculation of the neighbor node, there are 2 kinds of model, namely KNN (uniform) and KNN (distance).

If the weight is uniform, the value assigned to a point is calculated according to the simple majority vote of the nearest neighbors. However, in some cases, it is better to weight the neighbors so that the closer neighbors can make more contributions to the fit. Therefore, the second calculation method allocates weights proportional to the reciprocal of the distance from the query point.

2.5.2 Boosting

Boosting is a commonly used ensemble learning strategy. To get better knowledge about how boosting works and why this strategy is useful for clinical data, we used 3 kinds of boosting algorithm in the present study.

XGBoost (Optimized Parallel Tree Boosting) support CART (Classification and Regression Trees) and linear classifier at the same time with high flexibility. The XGBoost with linear classifier can be considered as Logistic regression or linear regression with L1 and L2 regularization. Regularization, which contains the number of leaf node on the tree and L2 regularization of the weight of the leaf node, is be used to balance the model complexity and avoid overfitting. Compared with some deep learning methods, XGBoost has simpler structure and greater interpretability.

Compared with XGBoost, LightGBM gets a breakthrough in memory consumption and calculation speed to some extent. Within histogram algorithm, we change the traversal over samples to traversal on histogram and get performance improvement. At the same time, to speed up further, we present Gradient-based One-Side Sampling (GOSS) to filter out those samples with small gradient. Considering the high calculating speed, the model can be applied to real-time operation (e.g., large-scale medical real-time data analysis).

CatBoost perform roughly between XGBoost and LightGBM, but in view of no parameters adjustment and ordered boosting application to avoid prediction offset, this model wins in simplicity and efficiency.

2.5.3 Bagging

Bagging, including ExtraTrees (Gini, Entr) and RandomForest (Gini, Entr), is also a very commonly used ensemble learning strategy.

As a set of many decision trees, RandomForest perform well on multivariate data due to the composite structure of processing discrete data and continuous data concurrently. There is no need to reduce dimension and choose any other feature selection tools. Also, RandomForest can measure the impact of different attributes, which can help understand multiple indicators of the patient. According to different nodes split type, we construct two kinds of model with Gini coefficient and entropy.

ExtraTrees (Extremely Randomized Trees) enable each base decision tree to use the same original dataset. Overall, ExtraTrees is quite similar to RandomForest except for higher variance and lower bias. Sometimes, ExtraTrees perform better in terms of regularization, so we chose to use this model for comparison in the medical tasks.

2.5.4 Stacking

For models, we consider combining some base learners, including Boosting or Bagging, to perform well. For datasets, we also set a specific training strategy to improve performance of the ensemble model.

Stacking aims at building a new model from several base models through feature transformation on training and testing sets. As shown in Figure 2, M represents a base model. We divide training set into N pieces and choose 1 piece for validation, while the other N-1 pieces are used to train the base model. After training, we get test and valid results. Then, we take an average of the N test results and get the test set feature transformation. We concatenate N valid results and get the valid set feature transformation.

For N base models, we proposed the method in Figure 3. In Figure 3, we concatenate N pairs of train-test and original train-test to get a new dataset and assign it to be the input of the N+1 models. Different from the normal stacking strategy with linear regression (model*) setting on high stacking layer to avoid overfitting, we still set base models on high stacking layer, which can help get better performance. Then we calculate suitable weight combination and get the prediction result from the N+1 models.

2.5.5 Simple deep learning

At first, we did not adopt any deep learning models because of the risk of overfitting and weak interpretability. But AutoGluon offers a different network, which applies different layers for categorical and numerical data.

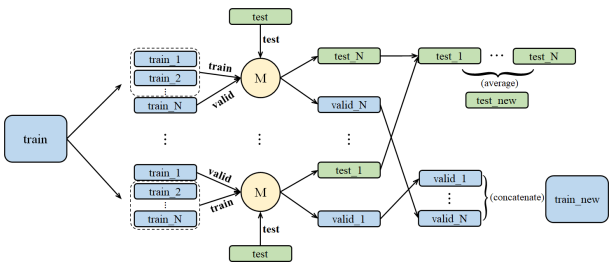

FIGURE 2
The stacking training process for a single model, including dataset segmentation and result integration.

For multivariate data, individual embedding layers enable the network to learn about each category feature individually before mixed variables to be used as input. In the next step, the embeddings of the category features are concatenated with the number features into a large vector. The vector will be fed into a 3-layer feedforward network and directly connected to the output predictions *via* a linear skip-connection. In AutoGluon, we adopted 2 neural network model based on PyTorch and Fastai v1 respectively.

2.6 Model discrimination and calibration

Accuracy, a good and intuitive evaluation index, is commonly used to evaluate the predictive performance of the machine learning models. Generally, higher accuracy means better prediction efficiency. And it can be written as:

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

(TP: True Positive, TN: True Negative, FP: False Positive, FN: False Negative)

Importance can be used to measure the degree to which different indicators contribute to the model. For example, if we delete one indicator and use the remaining indicators to train a model, the model prediction performance will decline. The degree of the decline, which is the magnitude of the decline in accuracy, is the value of the importance. Therefore, the higher the importance, the more important the indicator will be.

In the present study, different models were constructed using the database and randomly divided into training and validation sets at a ratio of 8:2. We also used K-fold cross-validation to validate the predicative performance of the machine learning model. Because K-fold cross-validation is easy to implement and had skill estimation with lower bias than other methods, it is often used to compare and select models for a given predictive modeling problem. The K-fold cross-validation was performed as follows: Divide the original dataset into K groups (the K value is 10 in our model); Select one group as the test dataset and the remaining groups as the train dataset; Fit a model with the train dataset and test the model on the test dataset; Retain the evaluation score (we use accuracy, precision and recall, and accuracy is the main indicator); Repeat the group selection until each group is tested. In summary, K-fold cross-validation averages K rounds of fitness in the prediction to derive the most accurate estimate of the model prediction performance.

3 Results

3.1 Patient characteristics and outcome

A total of 274 participants who underwent PA-TACE were recruited in this study, of which 142(51.8%) patients received once PA-TACE treatment. In the prediction model, twenty-eight predictors including clinicopathological characteristics, inflammatory-based prognostic biomarkers and clinical stages were analyzed. The baseline characteristics of all the participants

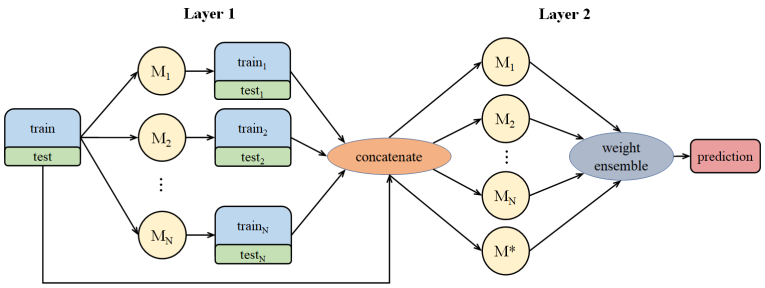

FIGURE 3
The stacking process of multiple models, including model weight distribution.

are shown in Table 1. At the end of follow-up, 137 (50.0%) patients presented HCC recurrence, and 56 (20.4%) patients died. The median follow-up time of the study was 20 (IQR: 9–30) months.

3.2 Prediction performance

The machine learning models included in our study were normal ML (KNN), Boosting (XGBoost; CatBoost; LightGBM), Bagging (Extra Trees; Random Forest), Stacking, and simple DL (DeepNN; Fastai). The discriminatory performance of the five models in overall mortality and HCC recurrence were assessed with the accuracy. Among the five models, the ensemble learning strategies, including Boosting, Bagging and Stacking, presented better predictive performance in terms of prognostic risk for HCC patients following PA-TACE (Tables 2, 3). Specially, the accuracy of the Stacking model in predicting overall mortality and HCC recurrence (test-accuracy: 0.8909, valid-accuracy: 0.9318; Table 2; test-accuracy: 0.7636, valid-accuracy: 0.8182; Table 3) was at the highest level in both training sets and validation sets. Moreover, the fitting time, prediction time and gain of five machine learning models were also compared, indicating that the Stacking model had relatively low time consumption and the best prediction performance (Tables 2, 3).

In time-dependent ROC analysis, the Boosting, Bagging, and Stacking model were found to perform well in predicting OS (1-year: 0.878, 0.871, 0.907; 2-year: 0.910, 0.919, 0.941; 3-year: 0.946, 0.930, 0.953; Figures 4A–C) and RFS (1-year: 0.784, 0.809, 0.812; 2-year: 0.845, 0.849, 0.847; 3-year: 0.789, 0.822, 0.834; Figures 4D–F) for HCC patients received PA-TACE. Moreover, patients were categorized into low- and high- risk groups based on the median risk score of the Stacking model. The low-risk group had significantly better overall survival and recurrence-free survival than the high-risk group ($P<0.001$; Supplemental Figures 1A, B). Therefore, KM curves indicated good discriminative ability of the Stacking model.

3.3 Models and variable importance

We also established the Stacking model to examine the variable importance of recurrence and overall mortality of the HCC patients after PA-TACE. The specific prediction performance of each predictor was measured using importance. The variables with the top 10 importance and P values are also shown in Table 4.

For overall mortality, the importance of BCLC Stage was 0.029341, substantially higher than scores of other variables, such as AFP (0.021429), ALB (0.014286), and frequency of PA-TACE (0.013106). For HCC recurrence, hsCRP/ALB (0.049635) was the most important variable, followed by MVI (0.029197), NLR (0.023358), and Tumor diameter (0.022628). Furthermore, BCLC Stage, hsCRP/ALB and frequency of PA-TACE were found to be relatively important variables in both overall mortality and recurrence, while MVI contributed more to the recurrence of the patients.

According to different cutoff values, continuous variables were converted into binary variables. Univariate Cox regression analyses were used to determine independent prognostic factors for OS and RFS. The results were generally consistent with the above results obtained from the Stacking model (Supplemental Table 1).

4 Discussion

To the best of our knowledge, our study was the first to utilize and compare different machine learning algorithms to analyze the RFS and OS outcomes of HCC patients following PA-TACE. Among the five machine learning models, the risk prediction model based on ensemble learning strategies, including Boosting, Bagging, and Stacking algorithms, presented better prediction performance for overall mortality and HCC recurrence. Specially, the fitting time, prediction time and gain of five machine learning models were also compared, indicating that the Stacking model had relatively low time consumption and the best prediction performance. In addition, according to time-dependent ROC analysis, the ensemble learning strategies were found to perform well in predicting both OS and RFS for the patients. In the present study, we also identified the important prognostic factors for postoperative outcomes. We found that BCLC Stage, hsCRP/ALB and frequency of PA-TACE were relatively important variables in both overall mortality and recurrence, while MVI contributed more to the recurrence of the patients.

Nowadays, increasing scoring systems have been developed to evaluate the prognosis of HCC and stratify patients. Most scoring systems have mainly selected significant clinical predictive indices

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TABLE 1 Baseline characteristics of the HCC patients.

Characteristics	Overall (n = 274)
Age (years), median (IQR)	56 (48-66)
BMI (kg/m^2), median (IQR)	22.4 (20.6-23.9)
Sex, n (%)	
Female	34 (12.4%)
Male	239 (87.2%)
Cirrhosis, n (%)	
Yes	197 (71.9%)
No	77 (28.1%)
BCLC stage, n (%)	
0/A	143 (52.2%)
B	96 (35%)
C	35 (12.8%)
Child-Pugh grade, n (%)	
A	204 (74.5%)
B	70 (25.5%)
HBV history, n (%)	
Yes	204 (74.5%)
No	70 (25.5%)
Frequency of PA-TACE, n (%)	
Once	142 (51.8%)
Twice	71 (25.9%)
Third	61 (22.3%)
Microvascular invasion, n (%)	
Positive	104 (38%)
Negative	170 (62%)
Tumor differentiation, n (%)	
Low	65 (23.7%)
Medium-high	209 (76.3%)
Maximum diameter of tumor (cm), median (IQR)	6 (4-9)
Tumor number, n (%)	
Single	179 (65.3%)
Multiple	95 (34.7%)
Portal vein tumor thrombus, n (%)	
Positive	41 (15%)
Negative	233 (85%)
Albumin (g/L), median (IQR)	38.3 (34.4-40.8)
AFP (ng/ml), median (IQR)	27.92 (4.0-538.7)
hsCRP (mg/L), median (IQR)	4.51 (1.23-15.46)
Total bilirubin (μmol/L), median (IQR)	17.9 (11.9-23.2)
NEUT counts (10^9/L), median (IQR)	3.44 (2.37-4.59)
LYM counts (10^9/L), median (IQR)	1.31 (0.97-1.77)
MONO counts (10^9/L), median (IQR)	0.45 (0.34-0.61)
PT (s), median (IQR)	11.9 (11.1-13.0)
Platelet (10^9/L), median (IQR)	157 (98-205)
SIRI, median (IQR)	1.13 (0.64-1.94)
SII, median (IQR)	294.1 (131.7-556.8)
PLR, median (IQR)	110.68 (77.17-176.62)
NLR, median (IQR)	2.57 (1.79-4.24)
PNI, median (IQR)	45.28 (40.45-48.73)
hsCRP/ALB, median (IQR)	0.12 (0.03-0.40)

HCC, hepatocellular carcinoma; BMI, body mass index; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALB, albumin; TACE, transarterial chemoembolization; hsCRP, high sensitivity C-reactive protein; NEUT, Neutrophils; LYM, lymphocyte; MONO, monocyte; PT, prothrombin time; SIRI, systemic inflammation response index; SII, systemic immune-inflammation index; PLR, platelet–lymphocyte ratio; MVI, Microvascular invasion; NLR, neutrophil–lymphocyte ratio; PNI, prognostic nutritional index.

through multivariate analysis, and constructed conventional Cox proportional risk models based on limited risk factors (32–34). However, in clinical studies, various risk factors often have nonlinear effects on recurrence-free survival, especially when they are used in cancer research (35–37). Therefore, the previous traditional models may fail to show the goodness of fitting or make accurate predictions. Machine learning could train algorithms to detect and recognize complex patterns and adapt to more complex nonlinear relationships, thus it might be superior than the traditional models in medical research (25). In our study, machine learning algorithms, including normal machine learning, Boosting, Bagging, Stacking, and simple deep learning were used and compared on RFS and OS outcomes of HCC patients received PA-TACE. The results showed that the Stacking algorithm, an ensemble learning strategy, presented relatively low time consumption, good discriminative ability, and the best prediction performance for the clinical outcomes. Therefore, this ensemble learning model, based on routine peripheral blood cell measurements and clinical characteristics, provides an easily accessible, effective, and intelligent approach for predicting OS and RFS in HCC patients received PA-TACE. Admittedly, the clinical practicability of this model needs further investigation.

In the present study, we also focused on the adaptability of different ensemble learning strategies to clinical data, so that other researchers could better apply specific ensemble learning models to specific clinical data through our comparative experiments. Considering the limited data size and complex data combinations of multiple attributes and dimensions used to predict the prognosis of HCC patients receiving PA-TACE, we therefore developed ensemble learning models including Boosting, Bagging, and Stacking algorithms, rather than sophisticated deep learning

TABLE 2 Predictive performance of different machine learning models for overall mortality.

	Test-accuracy	Valid-accuracy	Fit time(s)	Pred time(s)	Learning rate	N-estimators	Gain
Normal ML							
KNN (uniform)	0.8182	0.7273	0.0090	0.0385	–	–	-0.0727
KNN (distance)	0.8182	0.7273	0.0094	0.0447	–	–	-0.0727
Boosting							
XGBoost	0.8364	0.8864	0.8183	0.0141	0.1	10000	-0.0545
CatBoost	0.8727	0.9091	1.6993	0.0054	0.05	–	-0.0182
LightGBM	0.8909	0.9091	1.7005	0.3262	0.03	–	0
Bagging							
Extra Trees (Gini)	0.8545	0.8409	1.0892	0.1414	–	300	-0.0364
Extra Trees (Entr)	0.8364	0.8636	1.1028	0.1253	–	300	-0.0545
Random Forest (Gini)	0.8727	0.8409	1.2293	0.1288	–	100	-0.0182
Random Forest (Entr)	0.8364	0.8636	1.0606	0.1164	–	300	-0.0545
Stacking							
Weight Stacking	0.8909	0.9318	0.4780	0.0072	–	–	base
Simple DL							
DeepNN	0.8000	0.7955	1.1492	0.1010	0.0003	–	-0.0909
Fastai	0.7636	0.9091	2.1031	0.2925	0.01	–	-0.1237

ML, Machine Learning; KNN, K Nearest Neighbors; XGBoost, Optimized Parallel Tree Boosting; CatBoost, Gradient Boosting on Decision Trees; LightGBM, Gradient Boosting Framework that Uses Tree Based Learning Algorithms; Extra Trees, Extremely Randomized Trees; Entr, Entropy as Criterion; DL, Deep Learning; DeepNN, Deep Neural Network; Fastai, AutoML Framework.

strategies. These models do not have excessive overfitting, nor do they have a large number of hyperparameter to learn, which ensures a certain degree of generalization of the model. Moreover, K-fold cross-validation could be used to average K rounds of fitness in the prediction to derive the most accurate estimate of the model prediction performance. In conclusion, we believe that the ensemble learning model developed in our study could also be used to predict the prognosis in subsequent small sample clinical data with multiple attributes and dimensions.

The majority of liver cancers occur in cirrhotic livers with chronic inflammation, which creates a pro-inflammatory environment that promotes tumor formation and development (38–40). The importance of host inflammatory responses indicates the role of inflammatory indices in predicting clinical outcomes of the cancer patients (41). Therefore, apart from the laboratory tests and tumor characteristics, several inflammatory-based prognostic indices (NLR, PLR, SII, SIRI, hsCRP/ALB and PNI) were also included in this study. According to the feature importance analysis based on the Stacking model, interesting outcomes were obtained using these variables. Specifically, BCLC Stage, hsCRP/ALB and frequency of PA-TACE were relatively important variables in predicting both overall mortality and recurrence, while MVI contributed more to the recurrence of the patients. These findings are supported by the following studies.

Firstly, treatment allocation and prognostic stratification based on BCLC staging system, which is closely related to the prognosis of HCC, are currently the most widely used guidelines in clinical practice (42). For HCC patients, those in the early stages of BCLC could obtain good survival and low recurrence prognosis after curative resection (42, 43). In the present study, the predictive performance of the BCLC stage ranked first and fifth in overall mortality and recurrence of patients undergoing PA-TACE, which is in line with the results of previous studies.

Secondly, preoperative hsCRP is considered to be the most sensitive protein synthesized by the liver to detect systemic inflammation and could reflect the burden or development of HCC tumor cells (44, 45). In addition, preoperative albumin is an effective factor to reflect the nutritional status and liver function of the patients, and it is also a decisive factor of tumor cell immune response (46, 47). Studies have also shown that hsCRP/ALB and hsCRP/LYM have a powerful prognostic value for recurrence outcomes in HCC (48, 49). Therefore, for patients receiving PA-TACE, hsCRP/ALB might be a better prognostic indicator than other features, especially in predicting HCC recurrence.

Thirdly, the basic principle of postoperative TACE is to remove tumor cells that may have been shed from the resected tumor mass during hepatectomy and to eliminate small intrahepatic metastases that may not have been detected before or during the operation (50). Therefore, several studies have proved that postoperative adjuvant TACE could improve the prognosis of HCC patients (12, 13, 50). Specifically, the frequency of PA-TACE is also associated with a reduced HCC recurrence rate, improving the

TABLE 3 Predictive performance of different machine learning models for HCC recurrence.

	Test-accuracy	Valid-accuracy	Fit time(s)	Pred time(s)	Learning rate	N-estimators	Gain
Normal ML							
KNN (uniform)	0.5091	0.6591	0.0091	0.0362	–	–	-0.2545
KNN (distance)	0.5091	0.6364	0.0070	0.0388	–	–	-0.2545
Boosting							
XGBoost	0.6182	0.7273	0.8966	0.0262	0.1	10000	-0.1454
CatBoost	0.7091	0.7727	3.0586	0.0061	0.02	–	-0.0545
LightGBM	0.6727	0.7500	1.1155	0.0847	0.05	–	-0.0909
Bagging							
Extra Trees (Gini)	0.6727	0.7273	1.0993	0.1300	–	300	-0.0909
Extra Trees (Entr)	0.6909	0.7272	1.1894	0.1314	–	300	-0.0727
Random Forest (Gini)	0.7273	0.7727	1.2376	0.1302	–	300	-0.0363
Random Forest (Entr)	0.7455	0.7955	1.1472	0.1354	–	300	-0.0181
Stacking							
Weight Stacking	0.7636	0.8182	0.4634	0.0036	–	–	base
Simple DL							
DeepNN	0.6182	0.7727	2.0419	0.0716	0.0001	–	-0.1454
Fastai	0.7091	0.7500	1.9735	0.2300	0.01	–	-0.0545

HCC, hepatocellular carcinoma; ML, Machine Learning; KNN, K Nearest Neighbors; XGBoost, Optimized Parallel Tree Boosting; CatBoost, Gradient Boosting on Decision Trees; LightGBM, Gradient Boosting Framework that Uses Tree Based Learning Algorithms; Extra Trees, Extremely Randomized Trees; Entr, Entropy as Criterion; DL, Deep Learning; DeepNN, Deep Neural Network; Fastai, AutoML Framework.

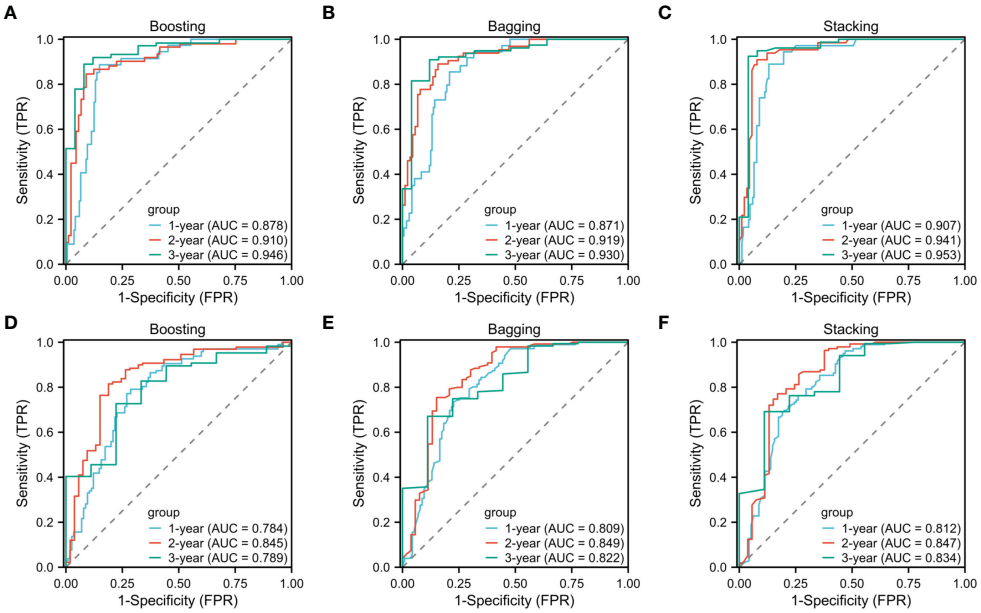

FIGURE 4
One-, two-, and three-year time-dependent ROC curves for overall survival **(A–C)** and recurrence-free survival **(D–F)** of the Boosting, Bagging and Stacking models.

TABLE 4 Variable importance of features included in the Stacking model to predict recurrence and overall mortality of the HCC patients after PA-TACE.

No.	Overall Mortality			HCC Recurrence		
	Features	Importance	P value	Features	Importance	P value
1	BCLC Stage	0.029341	0.000158	hsCRP/ALB	0.049635	0.004935
2	AFP	0.021429	0.000053	MVI	0.029197	0.000935
3	ALB	0.014286	0.000076	NLR	0.023358	0.000513
4	Frequency of PA-TACE	0.013106	0.001297	Tumor diameter	0.022628	0.001535
5	hsCRP/ALB	0.011992	0.007032	BCLC Stage	0.019708	0.000674
6	TB	0.011255	0.003995	Frequency of PA-TACE	0.017518	0.000594
7	Cirrhosis	0.010616	0.010858	Tumor differentiation	0.015328	0.002318
8	PT	0.009608	0.003369	Tumor number	0.014599	0.000935
9	PLR	0.008208	0.000121	AFP	0.013869	0.000744
10	Tumor number	0.008126	0.000132	SII	0.012409	0.008770

HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALB, albumin; TACE, transarterial chemoembolization; hsCRP, high sensitivity C-reactive protein; TB, total bilirubin; PT, prothrombin time; PLR, platelet–lymphocyte ratio; MVI, Microvascular invasion; NLR, neutrophil–lymphocyte ratio; SII, systemic immune-inflammation index.

long-term prognosis of patients (12). Furthermore, tumor dissemination and spread through microvessels might be one of the reasons for advanced tumor, tumor progression, and poor prognosis (51). Consistent with our results, MVI was also one of the unique parameters in many prognostic models for surgically resected HCC, including Early Recurrence After Surgery for Liver Tumor (ERASL), Singapore Liver Cancer Recurrence (SLICER) and Surgery-Specific Cancer of the Liver Italian Program (SS-CLIP) models (52–54).

This study also has several limitations. First, our model is primarily based on patients from one Chinese center with a limited sample size. It is necessary to validate our findings in further international, multicenter, large-scale studies. Second, the follow-up period is relatively short, long-term outcomes from prospective studies are critical to further extend the performance of our model.

5 Conclusion

In conclusion, we have utilized and compared models based on different machine learning algorithms and found that the ensemble learning models could better predict the risk of mortality and recurrence in individual HCC patients following PA-TACE. Specially, the Stacking algorithm presents relatively low time consumption, good discriminative ability, and the best predictive performance for clinical outcomes. Machine learning models could also help clinicians identify the important prognostic factors that are clinically useful in individualized patient monitoring and management.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by theHuman Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. All procedures were performed in accordance with the ethical guidelines of the Helsinki Declaration. The participants provided their written informed consent to participate in this study.

Author contributions

YL, ZW and YP were responsible for study conception and design, data acquisition, data analysis and drafting and revision of the manuscript. XH, JS were responsible for study conception and design, data analysis and drafting and revision of the manuscript. ZD, CL, YQ, YY and YS were responsible for data analysis and drafting and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1169102/full#supplementary-material

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Transarterial chemoembolization with or without multikinase inhibitors for patients with unresectable hepatocellular carcinoma: a systematic review and meta-analysis of randomized controlled trials

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Background: Randomized controlled trials (RCTs) testing the combination therapy of transarterial chemoembolization (TACE) plus multikinase inhibitor (MKI) in patients with unresectable hepatocellular carcinoma (HCC) have yielded inconsistent results.

Methods: In this work, a systematic review and meta-analysis was performed to compare the TACE+MKI combination therapy versus TACE monotherapy in HCC patients with time to progression (TTP) adopted as primary outcome.

Results: A total of 10 RCTs comprising 2837 patients receiving combination therapy (TACE plus sorafenib, brivanib, orantinib or apatinib) were included. TACE+MKI significantly prolonged TTP (hazard ratio [HR] 0.74, 95% CI 0.62-0.89, p=0.001) versus TACE monotherapy. Subgroup analysis suggested MKI administration before TACE might be preferable to post-TACE MKI for TTP. TACE+MKI also increased objective response rate (ORR) (risk ratio [RR] 1.17, 95% CI 1.03-1.32, p=0.01), but failed to improve overall survival (OS) (HR 0.98, 95% CI 0.86-1.13, p=0.82) and progression-free survival (PFS) (HR 0.75, 95% CI 0.50-1.12, p=0.16). The incidence of any adverse event (AE) did not significantly differ between TACE+MKI and TACE groups (RR 1.17, 95% CI 0.96-1.42, p=0.01), while serious AEs showed significant difference (RR 1.41, 95% CI 1.26-1.59, p<0.0001). Nevertheless, these AEs showing significant difference were mainly associated with MKI toxicities rather than TACE.

Conclusions: TACE+MKI combination therapy improved TTP and ORR but not OS and PFS in patients with unresectable HCC. Further high-quality trials are needed to verify these clinical benefits, and our findings could be very informative for future trial design.

KEYWORDS

transarterial chemoembolization, multikinase inhibitor, combination therapy, unresectable hepatocellular carcinoma, meta-analysis

1 Introduction

Liver cancer is the fourth leading cause of cancer-related death worldwide (1), and estimated to affect >1 million individuals annually by 2025 (2). Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and also the most lethal liver tumor with only 18% 5-year survival rate (1). Many etiologies contribute to the development of HCC, with viral hepatitis serving as the most prominent risk factor in the past. However, another pandemic is challenging its position due to effective viral treatment nowadays, for instance, the increasing incidence of NASH makes it already the fastest growing etiology of HCC [Rinaldi, 2021 #6300]. Currently, several treatment options have been adopted as standards of management for patients at different tumour stages, according to clinical practice guidelines (3–5). In principle, early-stage tumours are preferred candidates for liver transplantation, surgical resection or local ablation. Intermediate-stage tumours are potentially treatable by transarterial chemoembolization (TACE), whereas systemic therapy (i.e., sorafenib, atezolizumab plus bevacizumab) represents the mainstream for advanced HCC. All these therapies have contribute to a substantial increase in life expectancy (4–7). However, the overall prognosis remains dismal, owing to the preclusion of early diagnosis and curative treatment (8).

The assignment of TACE in intermediate-stage HCC is based on the evidence from two randomised controlled trials (RCTs) and a subsequent meta-analysis (9–11). Specifically, TACE is preferred to HCC patients at Barcelona Clinic Liver Cancer (BCLC) stage B, defined as being asymptomatic and liver-confined, without portal vein occlusion/thrombosis or extrahepatic spread, namely Child–Pugh class A or class B (5, 12). TACE can concentrate chemotherapeutic agents at the tumour site with higher concentrations than systemic chemotherapy, thus blocking the primary artery feeding the tumour. However, it increases tumour hypoxia, leading to the upregulation of hypoxia inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), and thus the increase of tumour angiogenesis, which are associated with a higher risk of extra-hepatic metastasis (13–15). Therefore, it has been proposed that combination therapy of TACE and anti-angiogenic agents should reduce tumour volume and vessel density, and thus improve clinical outcomes.

A number of multikinase inhibitors (MKIs) have been developed for systemic treatment of advanced HCC, since the first approval of sorafenib as first-line treatment. Sorafenib can inhibit a number of serine/threonine and tyrosine kinases (i.e., VEGFR, PDGFR), thereby exerting both anti-angiogenic and direct antitumour effects (16–18). Afterward, lenvatinib, a MKI against VEGFR and FGFR family, is demonstrated non-inferior to sorafenib in terms of overall survival (OS), and then approved for advanced HCC in the first-line setting (19). Additionally, many other oral MKIs [i.e., Brivanib (20), Orantinib (21), Apatinib (22)] showed preliminary efficacy and good safety profile for advanced HCC, whereas their roles in clinical practice have not been established yet.

Both TACE and MKI have been shown to improve survival, and meanwhile MKI in turn may lead to blockade of pro-angiogenic factors induced by TACE. As such, the rationale is clear to combine TACE with MKIs to improve clinical outcomes through inhibiting both tumour proliferation and revascularisation. Several small trials have shown that this combination is effective and safe in patients with unresectable HCC (23, 24). In contrast, most of RCTs testing this combination have failed to show clinical benefits (25–29). Nonetheless, a very recent phase III trial suggested that TACE plus sorafenib significantly improved progression-free survival (PFS) and time to progression (TTP), versus TACE alone (30). Hence, trials assessing the potential synergies between TACE and MKI have yielded inconsistent results. This systematic review and meta-analysis aimed to analyze the efficacy and safety of TACE/MKI combination as compared with TACE alone in patients with unresectable HCC.

2 Methods

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines and checklist for conducting this systematic review (31). The selection criteria regarding target population and outcomes was referenced to AASLD criteria for trial design and end points consensus conference (3). The project was prospectively registered at International Prospective Register of Systematic Reviews (PROSPERO No. CRD42022347259).

2.1 Search strategy

The systematic search was conducted using PubMed, EMbase, the Cochrane Library, and Web of Science to capture relevant

studies from inception to 18 Nov 2022, without language restriction. Combinations of the following keywords: hepatocellular carcinoma/HCC/liver cancer, sorafenib/lenvatinib/apatinib/sunitinib/axitinib/regorafenib/cabozantinib/donafenib/orantinib/brivanib/tyrosine kinase inhibitor/TKI/multikinase inhibitor/multi-kinase inhibitor/MKI, and chemoembolization/transarterial chemoembolization/TACE, were used in search (see details in Supplementary Table 1). The search strategy was designed and conducted by the authors (H.D, T.Y.W, Z.L).

2.2 Selection criteria

The records were independently assessed by the authors (H.D, T.Y.W, Z.L) based on the title/abstract and then full-text. Any disagreement between the authors was resolved by discussion to reach a consensus. Studies meeting the following inclusion criteria were considered of eligibility for meta-analysis: 1) trials were described as RCTs; 2) study patients were diagnosed with unresectable HCC, regardless of the kind of treatment they have experienced before; 3) trials comparing at least two different intervention arms (TACE plus MKI versus TACE alone); 4) one of the following outcomes must be included in each trial: TTP, OS, PFS, or objective response rate (ORR). We excluded studies that included participants with pregnancy or breastfeeding. We excluded studies with un-obtainable and unusable data.

2.3 Data extraction and quality assessment

The baseline characteristics and outcomes from eligible studies were independently extracted by the authors (H.D, T.Y.W, D.F.G) using a uniform extraction form. Study data included first author, year of publication, sample size, ECOG-PS (Eastern Cooperative Oncology Group performance status), BCLC (Barcelona Clinic Liver Cancer) stage, Child-Pugh score, etiology, follow-up, description of interventions, and type of outcomes (efficacy and safety).

Efficacy outcomes included OS, TTP and PFS, described as hazard ratio (HR) with 95% confidence interval (CI), and ORR. Safety outcomes included patients reporting any adverse event (AE), serious AEs, AE leading to dose interruption, and AE leading to treatment abort. Any disagreement between investigators was resolved by discussion. The risk of bias in the individual studies was assessed using the Cochrane risk of bias tool (32).

2.4 Statistical analysis

The primary outcome was TTP, and the secondary outcomes were OS, PFS, ORR and AEs. Meta-analysis was conducted using STATA 16.0 (Stata Corp LLC, TX, USA) using a random-effects model. The pooled HR with 95% confidence interval (CI) was calculated for time-to-event outcomes (TTP, OS and PFS) while pooled risk ratio (RR) was calculated for dichotomous data (ORR and AEs). Subgroup analyses were performed for efficacy outcomes based on the differences in the sequence of TACE and MKI administration. Sensitivity analysis was performed by excluding the study with significant heterogeneity if needed. Heterogeneity was assessed through I^2 statistic, with values over 50% indicating substantial heterogeneity. Publication bias was not evaluated as the number of studies included in the meta-analysis was too small.

3 Results

3.1 Study selection, characteristics and quality

Overall, a total of 901 unique studies were captured after deleting duplicates, of which 12 were identified as potentially relevant trials (Figure 1). After removing two ineligible studies, 10 reports were included for meta-analysis. The detail on fundamental characteristics of included RCTs was summarized in Supplementary Table 2. 10 trials included 2837 patients, with 1419 patients treated with TACE+MKI and 1418 treated with TACE+placebo or TACE alone (24–30, 33–35). At baseline, most patients had an ECOG PS of 0; the most common BCLC stage was B (intermediated stage), and most patients had a Child-Pugh Class of A. The etiologies varied across the studies, in which hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol dominated.

Among the 10 RCTs, four kinds of MKI were respectively combined with TACE (Figure 1), in which sorfenib was used in seven trials (25–27, 30, 33–35), while brivanib in BRISK-TA trial (28), orantinib in ORIENTAL trial (29), apatinib in the trial of Lu et al. (24). The detail on intervention characteristics and outcomes was summarized in Table 1. There were differences in the phase of trials, agent used, intervention program, follow-up, MKI dosage and primary endpoint across trials. Most of included studies were phase III, multi-centre trials [i.e. TACE 2 (26), BRISK-TA (28), ORIENTAL (29), TACTICS (30)]. The sequence and interval between drug administration and TACE performing varied, for instance, only three trials arranged MKI administration several days/weeks before first TACE [TACE 2 (26), SPACE (27) and TACTICS (30)], while other trials scheduled the first TACE session before MKI initiation. The median follow-up was specified in eight trials, ranging from the minimum 9.0 months in SPACE (27) to maximum 30.6 months in TACTICS (30). Among trials reporting the median dose or period of MKI, the maximum median dose of MKI (sorafenib, 660 mg) was shown in TACE 2 trial (26), while the maximum period of drug therapy (orantinib, 10.9 months) was shown in ORIENTAL trial (29). Regarding endpoints, TTP was adopted as the primary endpoint in four trials (25, 27, 33, 34), OS in two trials (28, 29), PFS in one trial (26), OS and PFS as the co-primary endpoints in one trial (30), ORR in one trial (24) and time-to-complete response in one trial (35).

Risk of bias assessment of included trials was based on the Cochrane risk of bias tool, and the detail was presented in Supplementary Figure 1. The risk of bias was generally low across trials. Specifically, all trials showed no risk of selection bias. However, three trials were open-label with potential risk of

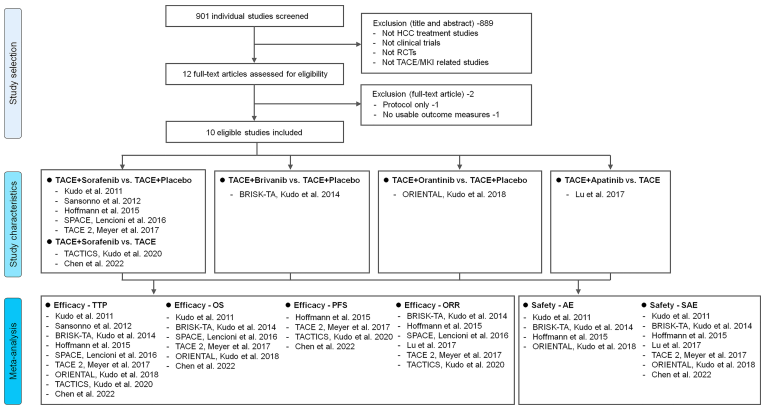

FIGURE 1
Study flowchart. Description of reasons for including/excluding studies from the current systematic review. Ten RCTs were finally included and four kinds of intervention pairs were compared in these trials (TACE+Sorafenib vs. TACE+Placebo/TACE, TACE+Brivanib vs. TACE+Placebo, TACE +Orantinib vs. TACE+Placebo, TACE+Apatinib vs. TACE). Meta-analysis of different efficacy outcomes (TTP, OS, PFS and ORR) and safety outcomes (AE and SAE) were conducted respectively. HCC, hepatocellular carcinoma; TTP, time to progression; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; AE, adverse event; SAE, serious adverse event; RCT, randomized controlled trial; TACE, transarterial chemoembolization; MKI, multikinase inhibitor.

TABLE 1 Intervention characteristics and study outcome measures of included studies in meta-analysis.

Study	Intervention	Patients included	Follow-up (mo)	MKI dose	Median dose & period (mo)	TTP (mo)		OS (mo)		PFS (mo)		ORR, n (%)
						Median	HR (95% CI)	Median	HR (95% CI)	Median	HR (95% CI)	
Kudo et al. 2011 (Eur J Cancer)	TACE first, then sorafenib	229	NA	400 mg twice daily	386 mg & 4.3	5.4	0.87 (0.70-1.09)	29.7	1.06 (0.69-1.64)	NA	NA	NA
	TACE first, then placebo	229	NA		786 mg & 5.0	3.7		NE		NA		NA
Sansonno et al. 2012 (Oncologist)	TACE first, sorafenib initiates 30 days after TACE	31	NA	400 mg twice daily	NA	9.2	0.40 (0.27-0.60)	NA	NA	NA	NA	NA
	TACE first, placebo initiates 30 days after TACE	31	NA		NA	4.9		NA		NA		NA
Kudo et al. 2014 (BRISK-TA, Hepatol)	TACE first, then brivanib no less than 48 hours, but no longer than 21 days after TACE	249	16.6	800 mg once-daily	NA & 6.0	12.0	0.94 (0.72-1.22)	26.4	0.90 (0.66-1.23)	NA	NA	120 (48)
	TACE first, then placebo	253	15.6		NA	10.9		26.1		NA		106 (42)
Hoffmann et al. 2015 (BMC Cancer)	TACE first, sorafenib was given 3 days before and after each TACE	24	10.7	400 mg twice daily	NA & 4.2	2.4	1.11 (0.39-3.16)	NA	NA	NA	1.26 (0.49-3.27)	5 (21)
	TACE first, then placebo	26			NA & 5.7	2.8		NA		NA		7 (27)
Lencioni et al. 2016 (SPACE, J Hepatol)	Sorafenib 3-7 days before first TACE	154	9.0	400 mg twice daily	566 mg & 5.3	5.6	0.80 (0.59-1.08)	NE	0.90 (0.61-1.33)	NA	NA	55 (36)
	Placebo 3-7 days before first TACE	153	9.1		791 mg & 6.8	5.5		NE		NA		43 (28)

(Continued)

TABLE 1 Continued

Study	Intervention	Patients included	Follow-up (mo)	MKI dose	Median dose & period (mo)	TTP (mo)		OS (mo)		PFS (mo)		ORR, n (%)
						Median	HR (95% CI)	Median	HR (95% CI)	Median	HR (95% CI)	
Lu et al. 2017 (Cancer Biol Ther)	TACE first, then apatinib 4 days after TACE	20	9.7	500 mg/day	NA	NA	NA	NA	NA	12.5	NA	7 (35)
	TACE alone	22			NA	NA		NA		6.0		2 (9)
Meyer et al. 2017 (TACE 2, Lancet Gastroenterol Hepatol)	Sorafenib 2-5 weeks before first TACE	157	20.7	400 mg twice-daily	660 mg & 4.0	10.9	0.88 (0.67-1.17)	21.0	0.91 (0.67-1.24)	34.0	0.99 (0.77-1.27)	56 (36)
	Placebo 2-5 weeks before first TACE	156			800 mg & 5.4	10.7		19.9		33.6		49 (31)
Kudo et al. 2018 (ORIENTAL, Lancet Gastroenterol Hepatol)	TACE first, then orantinib between days 3 and 28 after the first (and any subsequent) TACE	444	17.3	200 mg twice daily	NA & 10.9	2.9	0.86 (0.74-0.99)	31.1	1.09 (0.88-1.35)	NA	NA	NA
	TACE first, then placebo	444			NA & 12.3	2.5		32.3		NA		NA
Kudo et al. 2020 (TACTICS, Gut)	Sorafenib 2-3 weeks before first TACE	80	30.6	400 mg once daily before TACE, 800 mg once daily during TACE sessions	355 mg & 9.7	26.7	0.54 (0.35-0.83)	NA	NA	25.2	0.59 (0.41-0.87)	57 (71)
	TACE alone	76			NA	16.4		NA		13.5		47 (62)
Chen et al. 2022 (Hepatol Int)	TACE first, sorafenib was given 3 days before and after each TACE	29	23.8	400 mg/day	NA & 5.2	32.2	0.37 (0.18-0.77)	NE	0.68 (0.21-2.16)	24.8	0.46 (0.24-0.90)	NA
	TACE alone	30	NA		NA	14.5		31.0		14.5		NA

mo, months; TTP, time to progression; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval; NA, not available; NE, not estimable because of immaturity of data.
Data are n (%) for categories, and median for continuous data.

performance bias and detection bias (24, 30, 35), while others claimed double-blinded.

3.2 Efficacy outcomes

3.2.1 TTP

Our systematic review identified nine trials reporting TTP as either primary or secondary endpoint. Among them, seven trials evaluating TACE/sorafenib combination versus TACE alone. A meta-analysis with inclusion of these seven trials was conducted, and found significantly prolonged TTP in TACE+Sorafenib group versus TACE group (HR 0.67, 95% CI 0.52-0.87, p=0.003) (Supplementary Figure 2). Given that four trials scheduled sorafenib administration after TACE session while another three trials designed sorafenib plus following TACE, subgroup analyzes were conducted based on the administration sequence between sorafenib and TACE. The pooled results of four trials showed no significant difference between groups (HR 0.60, 95% CI 0.34-1.03, p=0.07), suggesting no clinical benefit of TTP from TACE combined with following sorafenib versus TACE alone. In contrast, the pooled results of another three trials demonstrated a significant difference in TTP between groups (HR 0.76, 95% CI 0.59-0.97, p=0.03). Therefore, the combination of sorafenib with TACE could improve TTP, and sorafenib administration prior TACE could be superior to that after TACE, in terms of TTP.

The remaining two trials scheduled brivanib or orantinib administration after TACE session (28, 29). A meta-analysis taking all nine trials together was conducted, and found a significant difference in TTP between TACE+MKI group and TACE group (HR 0.74, 95% CI 0.62-0.89, p=0.001) (Figure 2). This result was consistent with the pooled result above from seven sorafenib-trials, although the effect size differ slightly but not significantly. Besides, subgroup analyzes by prior or post TACE were consistent with the overall findings (HR 0.73, 95% CI 0.56-0.94, p=0.02; HR 0.76, 95% CI 0.59-0.97, p=0.03, respectively). In view of high heterogeneity across studies, a sensitivity analysis was conducted by removing the study of Sansonno et al. which was the source of heterogeneity, and the overall results were almost identical (HR 0.82, 95% CI 0.72-0.93, p=0.003) (Supplementary Figure 3).

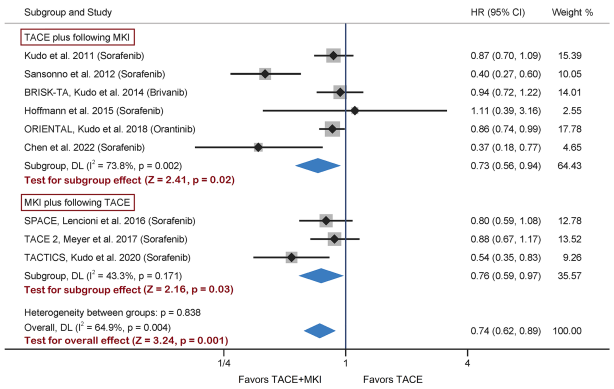

FIGURE 2
Meta-analysis of treatment effects of MKI in combination with TACE on TTP in patients with unresectable HCC. For subgroups analysis, 9 trials are divided into two classes based on TACE schedule: TACE plus following MKI & MKI plus following TACE. The MKI evaluated in these trials included sorafenib, brivanib and orantinib. The pooled HR of TTP was calculated by using a random-effects model, and the variance of the distribution of true effect sizes was estimated by means of the DerSimonian-Laird method. MKI, multikinase inhibitor; TACE, transarterial chemoembolization; TTP, time to progression; HR, hazard ratio.

Based on these results, the combination of TACE with MKI could improve TTP versus TACE alone, and scheduling MKI administration before TACE might be superior to that after TACE.

3.2.2 OS

Six of ten RCTs adopted OS as an endpoint (25–29, 35). Besides, sorafenib was administrated to patients in four trials while brivanib in BRISK-TA trial (28), and orantinib in ORIENTAL trial (29). Given the diversity of administrated drugs, we firstly performed a meta-analysis on the four trials evaluating the combination of sorafenib with TACE, and found no significant difference in OS between groups (Supplementary Figure 4). Subsequently, a meta-analysis integrating all six trials showed consistent results (HR 0.98, 95% CI 0.86-1.13, p=0.82) (Figure 3A). Besides, subgroup analysis found no difference in the effect sizes between the subgroup adopting prior TACE and that adopting post TACE (Figure 3A). Therefore, these results suggested that the combination of sorafenib with prior or post TACE failed to yield superior OS to TACE alone.

3.2.3 PFS

Four trials reporting PFS as an endpoint all designed sorafenib administration as adjuvant therapy to TACE (26, 30, 34, 35). We performed a meta-analysis on these four trials with inclusion of a total of 578 patients, demonstrating no significant difference in PFS between groups (HR 0.75, 95% CI 0.50-1.12, p=0.16) (Figure 3B). Additionally, subgroup analysis was conducted to examine whether the sequence between sorafenib administration and TACE operation may have affected PFS. Results by TACE plus following sorafenib or sorafenib plus following TACE were consistent with the overall findings (Figure 3B). Based on these results, the combination of sorafenib with TACE failed to yield superior PFS to TACE alone.

3.2.4 ORR

We identified six trials reporting ORR for inclusion into meta-analysis (24, 26–28, 30, 34). The ORR in sorafenib group ranged from 20.8% to 71.3% across trials. The pooled results of meta-analysis found that combination therapy significantly increased ORR versus TACE mono-therapy (risk ratio 1.17, 95% CI 1.03-1.32, p=0.01), although no significant difference were found from subgroup analysis (Figure 3C). The sensitivity analysis by using odds ratio as summary statistic yielded consistent results (odds ratio 1.33, 95% CI 1.07-1.67, p=0.012) (Supplementary Figure 5). The above results demonstrated that the combination of TACE and MKI could improve ORR, compared with TACE alone.

3.3 Safety outcomes

Table 1 summarized the AEs, AE leading dose interruption and AE leading treatment abort in either group of included studies. The pooled results from meta-analysis demonstrated that the incidence of any AE was not significantly different (risk ratio 1.17, 95% CI 0.96-1.42, p=0.11), although it was slightly lower in TACE group than in TACE+MKI group in all 4 trials (Figure 4A). Across the seven trials reporting serious AEs, their incidence varied strikingly (i.e., 0 to 48% in TACE+MKI groups) (24–26, 28, 29, 34, 35). Meta-analysis demonstrated that the incidence of serious AEs was significantly higher in patients receiving TACE+MKI than that receiving TACE alone (risk ratio 1.41, 95% CI 1.25-1.59, p<0.0001) (Figure 4B).

The most frequent, treatment-emergent AEs were abdominal pain, hand-foot skin reaction (HFSR), fatigue, pyrexia, anorexia, diarrhea, hypertension and thrombocytopenia in either group across studies. The incidence of these AEs in each trial was summarized in Table 2. The distribution and weighted means of incidence of each AE across trials were provided in Supplementary Figure 4. They were ranked as abdominal pain > HFSR > fatigue > pyrexia > anorexia > diarrhea > hypertension > thrombocytopenia in TACE+MKI group, while abdominal pain > pyrexia > fatigue > anorexia > diarrhea > thrombocytopenia > hypertension > HFSR in TACE group, according to the weighted means of incidence. Additionally, meta-analysis was performed on each kind of AEs to explore their differences between groups (Supplementary Figure 6). The pooled results demonstrated that the incidence of HFSR, fatigue, anorexia, diarrhea, hypertension and thrombocytopenia was significantly higher in TACE+MKI group than TACE group, respectively, while there was no significant difference in the incidence of abdominal pain and pyrexia between groups (Supplementary Figures 6, 7).

4 Discussion

As a kind of local therapeutic-strategy, TACE has become the standard of care for patients with intermediate stage HCC. However, the repetition of TACE results in two major problems: deteriorated liver function and increased tumour angiogenesis (13–

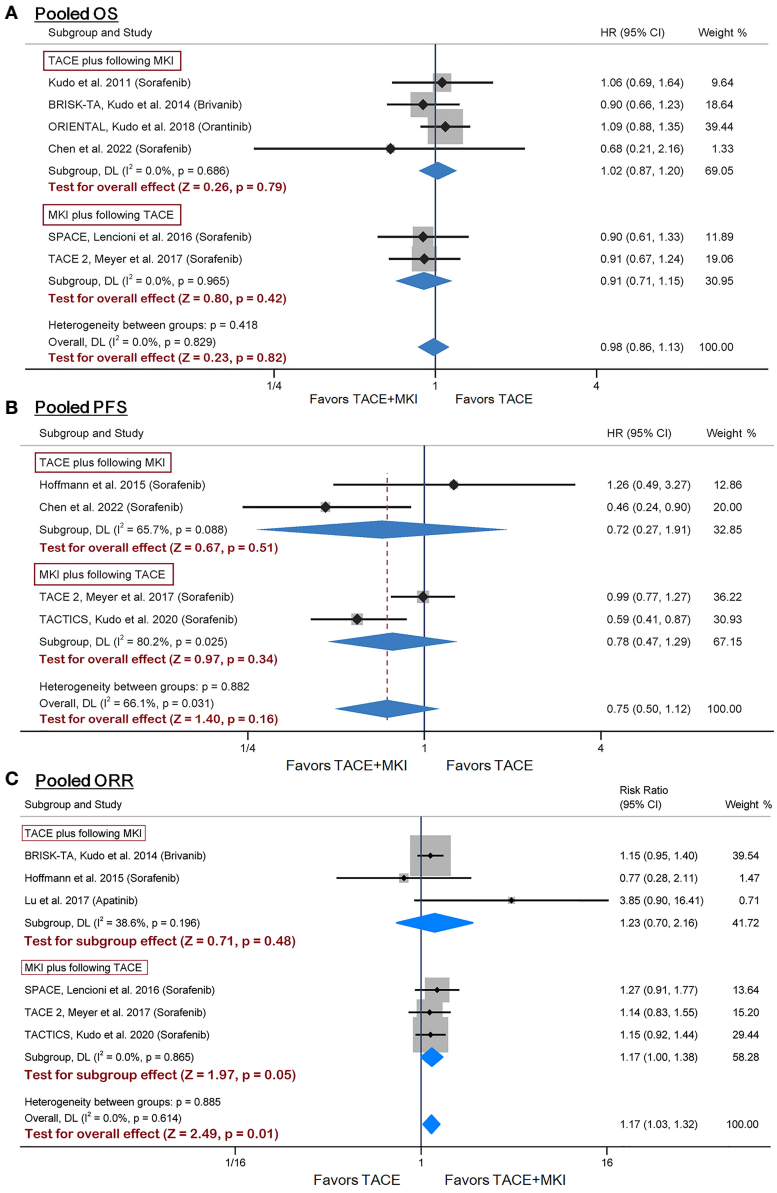

FIGURE 3
Meta-analysis of treatment effects of MKI in combination with TACE on OS **(A)**, PFS **(B)** and ORR **(C)** in patients with unresectable HCC. For subgroups analysis, trials are divided into two classes based on TACE schedule: TACE plus following MKI & MKI plus following TACE. The MKI evaluated in these trials included sorafenib, brivanib and orantinib. The pooled HR or RR was calculated by using a random-effects model, and the variance of the distribution of true effect sizes was estimated by means of the DerSimonian-Laird method. MKI, multikinase inhibitor; TACE, transarterial chemoembolization; OS, overall survival; PFS, progression- free survival; ORR, objective response rate; HR, hazard ratio; RR, risk ratio.

15). The tumour angiogenesis is attributed to the acute hypoxia caused by TACE which consequently leads to the upregulation of some kinases, such as VEGF and PDGF. As such, it seems promising to schedule MKI administration as adjuvant therapy to TACE to improve clinical outcomes with the assistance of its both antiangiogenic and direct antitumour effects. To date, many RCTs have evaluated the combination of TACE with MKI (i.e. sorafenib, brivanib, orantinib and apatinib) in patients with unresectable HCC, however, yielded inconsistent results (24–30, 33–35).

Several meta-analyses have been done on TACE/sorafenib combination. The meta-analysis of Wang et al. (36) included five comparative studies (only two RCTs) found that TACE+sorafenib improved TTP (HR 0.61, 95% CI 0.39-0.95; pooled result of three studies) but failed to improve OS (HR 0.79, 95% CI 0.54-1.16; pooled result of three studies). However, their findings were limited by the small number of included studies, high heterogeneity across the studies, and especially the mixed RCTs, prospective and retrospective studies. Two subsequent network meta-analyses respectively included 5 and 6 trials to compare TACE+sorafenib versus TACE (37, 38). Whereas, some of these included trials they claimed RCTs turned out to be nonrandomized which drastically challenged the credibility of their findings. A latest network meta-

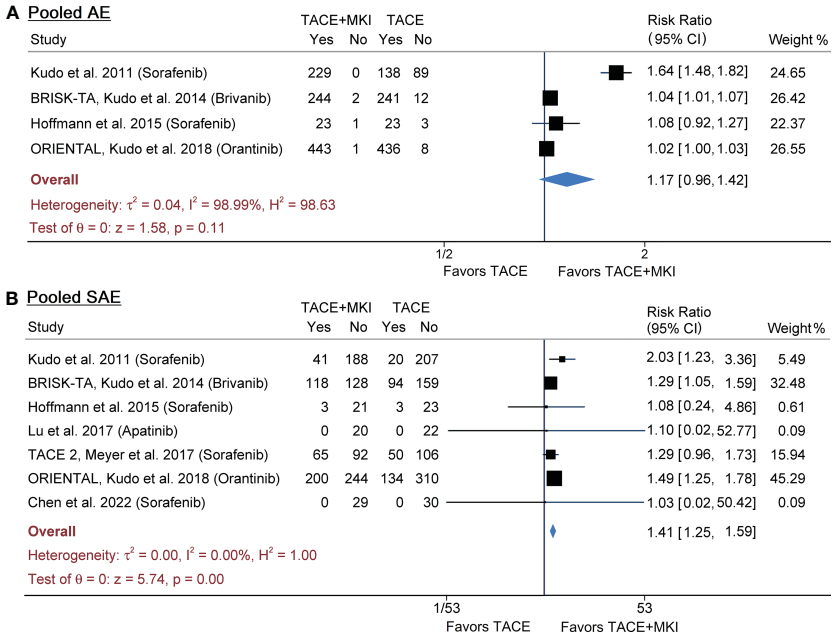

FIGURE 4
Meta-analysis of AEs **(A)** and SAEs **(B)** of MKI in combination with TACE in patients with unresectable HCC. The MKI evaluated in these trials included sorafenib, brivanib and apatinib. The pooled risk ratio was calculated by using a random-effects model. AE, adverse event; SAE, serious adverse event; MKI, multikinase inhibitor; TACE, transarterial chemoembolization.

analysis conducted by Zhang et al. (39) found that TACE plus TKIs (apatinib, lenvatinib, or sorafenib) significantly benefited OS (HR 2.09, 95% CI 1.50-2.91; HR 2.72, 95% CI 1.37-5.59; and HR 1.46, 95% CI 1.20-1.75, respectively) and PFS (HR 1.67, 95% CI 1.12-2.63; HR 2.99, 95% CI 1.72-5.28; and HR 1.54, 95% CI 1.17-2.08, respectively), compared with TACE monotherapy. However, only five trials were RCTs while others were cohort studies among the included 41 studies. Additionally, the outcome measures of TTP and AEs were not evaluated in this meta-analysis.

This meta-analysis provides currently the most comprehensive synthesis of comparative data from RCTs on the efficacy and safety of TACE/MKI combination versus TACE. We found that MKI as adjuvant therapy to TACE improved TTP and ORR, but not OS or PFS. Specifically, the meta-analysis with inclusion of nine trials found that TACE+MKI significantly prolonged TTP versus TACE alone, and subgroup analysis by prior or post TACE yielded consistent results. Besides, sensitivity analysis by removing the heterogenous study found that TTP did not differ significantly in subgroup of TACE plus following MKI while it differ significantly in subgroup of MKI plus following TACE. In regard to sorafenib, the meta-analysis of seven RCTs demonstrated that combination therapy significantly increased TTP, and subgroup analysis suggested that sorafenib administration prior to TACE could be superior to that after TACE regarding TTP. Likewise, Overall, the combination of TACE with MKI could result in longer TTP than TACE alone in patients with unresectable HCC, and scheduling MKI administration before TACE session might be superior to that after TACE operation.

MKI administration is designed to suppress tumour angiogenesis induced by TACE, thus timing for drug administration, relative to TACE, represents a key to maximize its efficacy. The ORIENTAL trial provided a clue that patients in orantinib group with a VEGF-C concentration below the median value showed significantly prolonged time to TACE failures (29), indicating that low VEGF level might contribute to a favourable clinical outcome. Since serum VEGF reaches maximum concentration on day 1 after TACE (13), MKI may exert the greatest effects when administered immediately after or even before TACE. Correspondingly, SPACE trial firstly tested the efficacy of sorafenib plus following TACE in which sorafenib was administrated 3-7 days before the first TACE (27). In particular, this combination improved TTP according to the predefined statistical threshold (HR 0.79, one-sided p= 0.072), despite no difference in median TTP between groups (27). The subsequent TACE 2 with similar study design yet failed to provide positive result for TTP (26). In contrast, the latest TACTICS trial reported a significantly longer TTP in TACE+Sorafenib group than TACE group (26.7 vs. 20.6 months, p=0.02) and also a significantly longer PFS (25.2 vs. 13.5 months, p=0.006) (30). These favourable outcomes may be due to pre-treatment with sorafenib 2-3 weeks before the initial TACE, as well as the long median duration of sorafenib treatment (38.7 weeks). To sum up, MKI administration before TACE could be preferable to post-TACE MKI for prolonging TTP, which was evidenced by our findings. However, the optimal timing for MKI administration has not reach a consensus, thus further high-quality

TABLE 2 Summary of adverse events in either group of included studies in meta-analysis.

Study	Intervention	Patients included	AE, n (%)											AE→ dose interruption	AE→ treatment abort
			Any	Grade ≥3	Serious AE	Abdominal pain	HFSR	Fatigue	Pyrexia	Anorexia	Diarrhoea	Hypertension	Thrombocytopenia		
Kudo et al. 2011	TACE +Sorafenib	229	229 (100)	NA	41 (18)	29 (13)	188 (82)	46 (20)	37 (16)	45 (20)	71 (31)	71 (31)	57 (25)	163 (71)	93 (41)
	TACE +Placebo	227	138 (61)	NA	20 (9)	21 (9)	16 (7)	34 (15)	25 (11)	18 (8)	11 (5)	16 (7)	5 (2)	27 (12)	13 (6)
Sansonno et al. 2012	TACE +Sorafenib	40	NA	NA	NA	NA	4 (10)	9 (23)	NA	3 (8)	4 (10)	6 (15)	NA	8 (5)	9 (22)
	TACE +Placebo	40	NA	NA	NA	NA	0 (0)	3 (8)	NA	4 (10)	3 (8)	4 (10)	NA	0 (0)	0 (0)
Kudo et al. 2014 (BRISK-TA)	TACE +Brivanib	246	244 (>99)	172 (69)	118 (48)	90 (37)	77 (31)	101 (41)	93 (38)	106 (43)	88 (36)	116 (47)	58 (24)	68 (28)	98 (40)
	TACE +Placebo	253	241 (95)	109 (43)	94 (37)	101 (40)	5 (2)	59 (23)	115 (46)	57 (23)	25 (10)	29 (11)	42 (17)	7 (3)	46 (18)
Hoffmann et al. 2015	TACE +Sorafenib	24	23 (92)	12 (50)	3 (13)	0 (0)	7 (29)	5 (21)	0 (0)	0 (0)	9 (38)	0 (0)	13 (54)	6 (25)	6 (25)
	TACE +Placebo	26	23 (96)	4 (16)	3 (12)	0 (0)	1 (4)	5 (21)	0 (0)	0 (0)	3 (12)	0 (0)	14 (56)	2 (8)	1 (4)
Lencioni et al. 2016 (SPACE)	TACE +Sorafenib	153	NA	NA	NA	92 (60)	71 (46)	66 (43)	59 (39)	47 (31)	81 (53)	46 (30)	NA	133 (87)	129 (84)
	TACE +Placebo	151	NA	NA	NA	93 (62)	10 (7)	50 (33)	52 (34)	31 (21)	26 (17)	25 (17)	NA	93 (61)	63 (42)
Lu et al. 2017	TACE +Apatinib	20	NA	3 (15)	0 (0)	9 (45)	11 (55)	NA	15 (75)	NA	4 (20)	16 (80)	NA	NA	3 (15)
	TACE	22	NA	0 (0)	0 (0)	12 (55)	0 (0)	NA	17 (77)	NA	1 (5)	1 (5)	NA	NA	0 (0)
Meyer et al. 2017 (TACE 2)	TACE +Sorafenib	157	NA	NA	65 (41)	93 (59)	65 (41)	127 (81)	NA	53 (34)	87 (55)	NA	NA	NA	30 (19)
	TACE +Placebo	156	NA	NA	50 (32)	89 (57)	13 (8)	122 (78)	NA	52 (33)	49 (31)	NA	NA	NA	16 (10)
Kudo et al. 2018 (ORIENTAL)	TACE +Orantinib	444	443 (>99)	NA	200 (45)	317 (71)	43 (10)	101 (23)	264 (59)	209 (47)	123 (28)	59 (13)	53 (12)	160 (36)	96 (22)
	TACE +Placebo	444	436 (98)	NA	134 (30)	292 (66)	51 (11)	92 (21)	284 (64)	149 (34)	70 (16)	57 (13)	48 (11)	37 (8)	49 (11)
Kudo et al. 2020 (TACTICS)	TACE +Sorafenib	77	NA	NA	NA	NA	41 (53)	19 (25)	15 (20)	11 (14)	11 (14)	40 (52)	67 (87)	77 (100)	2 (3)

(Continued)

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TABLE 2 Continued

Study	Intervention	Patients included	AE, n (%)											AE→ dose interruption	AE→ treatment abort
			Any	Grade ≥3	Serious AE	Abdominal pain	HFSR	Fatigue	Pyrexia	Anorexia	Diarrhoea	Hypertension	Thrombocytopenia		
Chen et al. 2022	TACE	71	NA	NA	NA	NA	0 (0)	7 (10)	18 (25)	8 (11)	0 (0)	28 (39)	53 (75)	NA	2 (3)
	TACE +Sorafenib	29	NA	5 (26)	0 (0)	0 (0)	17 (59)	6 (21)	14 (48)	2 (7)	6 (21)	3 (10)	12 (41)	0 (0)	0 (0)
	TACE	30	NA	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)	11 (37)	3 (10)	0 (0)	1 (3)	7 (23)	0 (0)	0 (0)

AE, adverse event; HFSR, Hand- foot skin reaction; TACE, transarterial chemoembolization; NA, not available.

trials are needed to verify the clinical benefit from MKI pre-treatment combined with TACE.

There has been no consensus regarding the primary endpoints in TACE/MKI combination trials. OS is objective and clinically relevant serving as the sole robust endpoint. The phase III trials BRISK-TA and ORIENTAL chose OS as the primary endpoint (28, 29). However, OS measure requires long follow-up time to capture the events (40), thus being a critical limitation when evaluating interventions for HCC at early or intermediate stages. Additionally, in particular of MKI/TACE combination trial, the high rate of crossover to MKI might obscure any benefit of the combination if OS is adopted as the primary endpoint (26). Therefore, several surrogate endpoints, such as PFS, TTP and ORR, have been proposed although lacking of adequate validation. For these endpoints, tumour response is mostly assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria or modified RECIST (mRECIST), but TACTICS trial adopted Response Evaluation Criteria in Cancer of the Liver (RECICL) to define progression. Although TTP has been suggested of weakness for predicting clinically relevant improvement in OS, it indeed has its own strong point in capturing the implied clinical benefit from combination therapy: the differences in TTP are not masked by the second treatment despite the crossover efficacy in combination therapy. Consistently, among the included 10 trials, TTP was chosen as the primary endpoint in four trials (25, 27, 33, 34), and as the secondary endpoint in five trials (26, 28–30, 35). Therefore, TTP was selected as the primary outcome in our meta-analysis.

The combination of TACE with MKI was clinically safe cross trials. The most frequent AEs related to TACE are typical of post-embolization syndrome, such as abdominal pain, pyrexia and nausea (41). Regarding MKI, the most common AEs are HFSR, diarrhoea and hypertension. Although some AEs were more frequently observed in the TACE+MKI group than TACE group, the addition of MKI didn't seem to increase toxicity associated with TACE. It was evidenced by no significant difference in the incidence of abdominal pain and pyrexia between groups in our meta-analysis. Furthermore, the major differences were related to the well-known toxicities of MKI, as evidenced by that significantly higher incidence of HFSR, fatigue, anorexia, diarrhea, hypertension and thrombocytopenia was found in TACE+MKI group.

Some limitations should be acknowledged in our meta-analysis. First, the number of included studies for meta-analysis (range 4-9 comparative studies) was small. Second, there were differences in the tools for defining tumour progression across trials, for instance, RECIST in TACE 2 trial (26), mRECIST in BRISK-TA trial (28), while RECICL in TACTICS trial (30). Third, specific data for subset analysis by etiology or region were not available among trials, while the effects of regional or etiologic variability on outcomes might be latent. Forth, HCC patients may also present several comorbidities beyond the hepatic problem itself which may alter outcomes, whereas this work failed to evaluate the comorbidity burden due to the varied exclusion criteria across studies and unavailable data. Finally, the trials included were heterogeneous, comprising the differences in study population, clinical characteristics (i.e., ECOG-PS, BCLC stage and Child-Pugh stage), the variety of MKI (sorafenib, brivanib, orantinib and apatinib), as well as the different

timings of MKI administration, which might impact the treatment efficacy and cause bias in the pooled results.

5 Conclusions

In summary, our meta-analysis found that the combination of TACE with MKI could result in improved TTP and ORR in patients with unresectable HCC versus TACE alone. Besides, pre-treatment with MKI, relative to TACE, might lead to a better outcome of TTP than post-TACE MKI treatment. However, this combination failed to improve OS and PFS. The addition of MKI doesn't seem to increase toxicity associated with TACE. Some AEs, occurred more frequently in the combination group, were associated with the well-known toxicities of MKI. Despite some limitations in this work, we provide updated and comprehensive evidence on the efficacy and safety of TACE/MKI combination therapy, and our findings could be very informative for future clinical trial design.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

ZL, TW and JW: conceptualization and supervision. ZL and HD: writing. ZL and DG: revision. DG, PZ and BQ: software and methodology, data curation. HD, QW and BQ: investigation and formal analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1139025/full#supplementary-material

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Endovascular brachytherapy with iodine-125 seed strand for extensive portal vein tumor thrombus in patients with hepatocellular carcinoma

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Objective: The aim of this study is to investigate the feasibility and effectiveness of endovascular brachytherapy with iodine-125 (I-125) seed strand for the treatment of extensive portal vein tumor thrombus (PVTT) in hepatocellular carcinoma (HCC) patients.

Methods: A total of 40 HCC patients complicated by extensive PVTT who received I-125 seed strand implantation from January 2015 to December 2022 in our center were analyzed retrospectively. Endpoints included technical success rate, concurrent therapies, overall survival time, and complications. Multivariate and subgroup analyses were conducted for overall survival.

Results: The successful rate of operation was 100%, and there was no operation-related death. A total of 37 patients received single I-125 seed strand implantation, and three patients received double I-125 seed strand implantation. A total of 23 patients received a concurrent therapy: transarterial chemoembolization (TACE) combined with systematic treatment (n = 6), TACE alone (n = 10), and systematic treatment alone (n = 9). At a median follow-up of 3.5 (interquartile range (IQR), 2~8.5) months, the median overall survival (OS) of all patients was 92 days (95% confidence interval (CI): 77~108). In the subgroup analysis, the median OS was 128 days (95% CI: 101~155 days) in the I-125 seed strand implantation plus systematic treatment group and was longer than that (75 days (95% CI: 36~114) of the I-125 seed strand alone group (p = 0.037). Multivariate analysis revealed that no systematic treatment was an independent risk factor affecting the prognosis in this study. Six patients died of upper gastrointestinal bleeding: four patients in the I-125 seed strand alone group and two patients in the combination of I-125 seed strand with systematic treatment group.

Conclusions: The study shows that endovascular brachytherapy with I-125 seed strand implantation is a safe and effective treatment method for extensive PVTT in HCC patients. The combination of I-125 seed strand implantation and systematic treatment can prolong the survival time.

KEYWORDS

hepatocellular carcinoma, extensive portal vein tumor thrombus, iodine 125 seeds strand, endovascular brachytherapy, systematic treatment

Introduction

Hepatocellular carcinoma (HCC) often invades the intrahepatic portal vein and extends to the major and opposite side branch of the portal vein, thus forming portal vein tumor thrombus (PVTT). The proportions of HCC patients with PVTT range from 13% to 45% in different countries (1). HCC with PVTT is associated with a poor prognosis, and the degree of PVTT correlates with the prognosis (2, 3). Radiation therapy as an alternative therapy for treating PVTT was recommended in a few guidelines (4, 5). However, external radiation therapy may cause radiation-induced liver disease, especially for patients with a cirrhotic background (6). Recently, several reports have shown that brachytherapy using portal vein irradiation stent or stenting combined with I-125 seed strand was a safe and effective treatment method for HCC with major portal vein tumor thrombus (7–9). However, the blood flow of the portal vein cannot be recovered through stenting among HCC patients with extensive PVTT (tumor thrombus in the bilateral first portal branches with complete occlusion and major portal vein invasion, with or without the superior mesenteric vein invasion). Extensive PVTT with more tumor thrombus burden is more likely to cause portal hypertension and gastrointestinal bleeding. In our center, I-125 seed strand implantation has been performed for patients with extensive PVTT who are unsuitable for portal vein irradiation stent implantation. In this study, we conducted a retrospective study to investigate the feasibility and effectiveness of I-125 seed strand for the treatment of extensive PVTT in HCC patients.

Materials and methods

Patients

This retrospective study included 40 HCC patients with extensive PVTT who underwent I-125 seed strand implantation from January 2015 to December 2022. The diagnosis of HCC was according to the American Association for the Study of Liver Diseases practice guidelines or the European Association for the Study of the Liver clinical practice (10, 11). PVTT was confirmed by the presence of enhancement of a liver lesion mass expanding into the portal vein in the arterial phase and a low-attenuation intraluminal filling defect in the portal phase on enhanced CT or MRI (12). Extensive PVTT refers to tumor thrombus in the bilateral first portal branches with complete occlusion and major portal vein invasion, with or without the superior mesenteric vein invasion. Inclusion criteria: a) patients were older than 18 years, b) Child–Pugh grade A or B, c) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0~2, and d) HCC patients with extensive PVTT. The exclusion criteria were as follows: a) Child–Pugh grade C, b) ECOG PS 3, and c) expected life span of less than 1 month. All patients had signed an informed consent form for I-125 seed strand implantation.

I-125 seed strand

The diameter and length of the titanium capsule were 0.8 and 4.5 mm. I-125 seed activity was 0.6 mCi with a half-life of 59.6 days. The number (n) of I-125 seeds was determined by the length of the PVTT (L mm). N = L/4.5 + 4. I-125 seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China) were enveloped in a 4 Fr angiocatheter, in which both ends were sealed by heat.

I-125 seed strand implantation

The operation was performed under local anesthesia by experienced interventional radiologists with more than 20 years of experience. A Chiba needle (Cook Medical, Bloomington, IN, USA) was used to puncture the second-order portal vein with color Doppler ultrasound guidance. A 6-Fr outer sleeve (Cook, Inc.) was inserted into the portal vein, followed by a 5-Fr sheath (Cordis, Miami Lakes, FL, USA). The I-125 seed strand was delivered to the target position through the 5-Fr sheath. The puncture tract then was occluded by coils or gelatin sponge (Figure 1).

Follow-up

Complete blood count, liver function, alpha-fetoprotein (AFP), CT, and MRI data were collected. The primary outcome measurement was overall survival time, which was defined as the time from I-125 seed strand implantation to the date of death or last follow-up. Follow-up was censored at the occurrence of death or the end of the study period (31 May 2023). Treatments of intrahepatic parts of HCC were also collected. Complications were

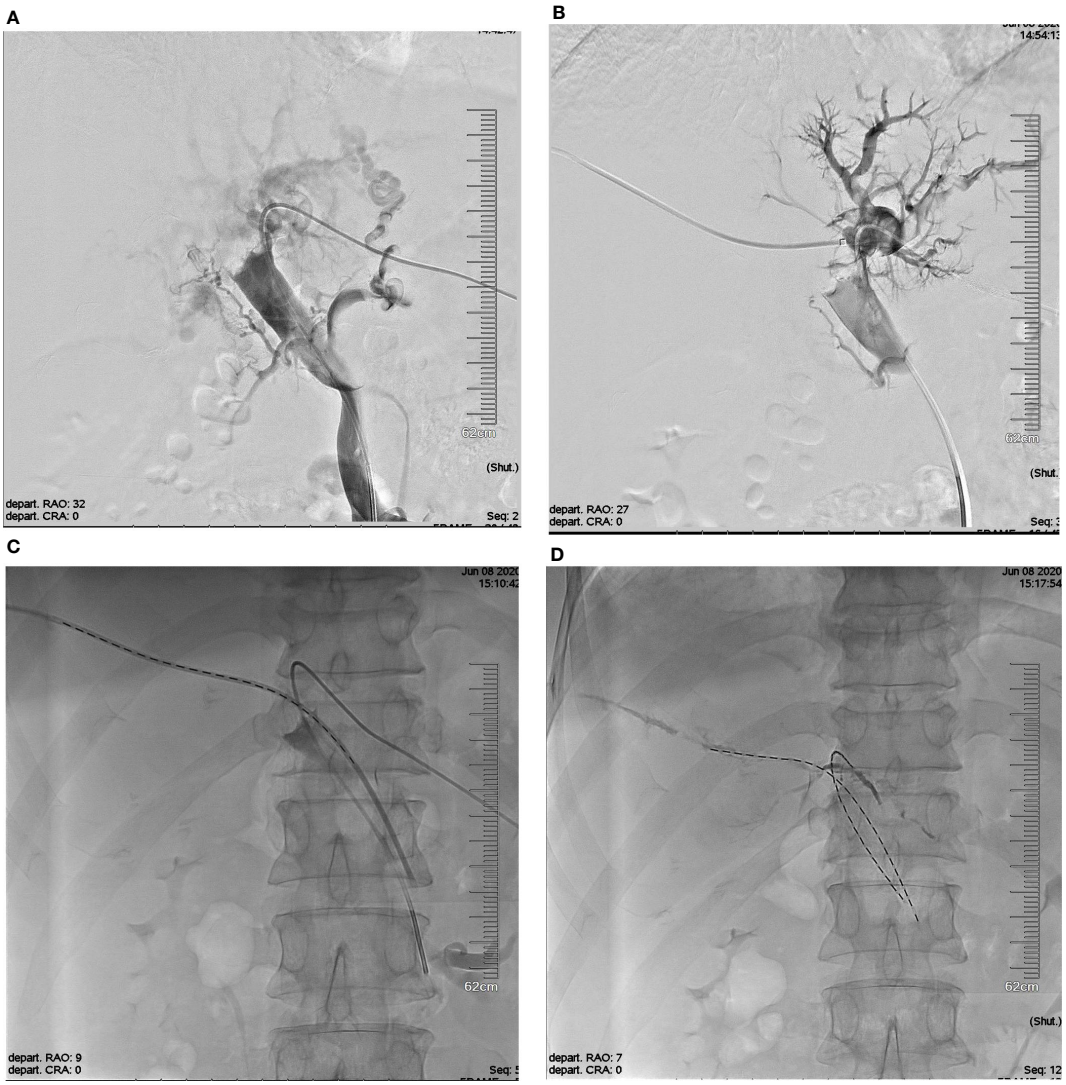

FIGURE 1
The schematic diagram of I-125 seed strand Implantation. **(A)** Photograph showing the tumor thrombus in the bilateral first portal branches with complete occlusion and major portal vein invasion. **(B)** Establishment of another I-125 seed strand implantation channel via right portal vein. **(C)** The double I-125 seed strands were delivered to the target position through the 5-Fr sheath. **(D)** The double I-125 seed strands were fixed in the PVTT. PVTT, portal vein tumor thrombus.

determined by the Common Terminology Criteria for Adverse Events 5.0 (13).

Statistical analysis

Data were presented in mean ± standard deviation or descriptive statistics. All statistical analyses were performed using R (version 3.6.3). The chi-square test, Wilcoxon rank sum test, or Fisher's exact test was used to compare the differences in hematological indices between preoperative and postoperative. Multivariate analysis was performed using the Cox proportional hazards model including variables with *p*-values less than 0.15 in univariate analysis. The time-to-event variables were estimated using the Kaplan–Meier method and compared by the log-rank test. *p*-Values less than 0.05 were considered statistically significant.

Results

Patient characteristics

According to the inclusion and exclusion criteria, a total of 40 patients with HCC complicated with extensive PVTT were included: 39 male and 1 female (Table 1). The average length of PVTT far from the junction of the left/right portal vein was 6.3 ± 2.9 cm. In this study, 39 cases were complicated with chronic hepatitis B virus infection. A total of 37 patients received single I-125 seed strand implantation, and three patients received double I-125 seed strands. There is no active treatment for intrahepatic parts of HCC. A total of 23 patients received a concurrent therapy: transarterial chemoembolization (TACE) combined with systematic treatment (n = 6), TACE alone (n = 10), and systematic treatment alone (n = 9). Gelatin sponge embolization

TABLE 1 Baseline characteristics of patients.

Variable	n (%)
Sex	
Male	39 (97.5%)
Female	1 (2.5%)
Age	
≤65	28 (70%)
>65	12 (30%)
Location of intrahepatic tumor	
Single liver lobe	21 (52.5%)
Whole liver lobe	19 (47.5%)
Tumor burden	
<50%	19 (47.5%)
≥50%	21 (52.5%)
Tumor type	
Infiltrative	29 (72.5%)
Nodular	11 (27.5%)
Extra-hepatic disease	
Yes	7 (17.5%)
None	33 (82.5%)
AFP	
<400 ng/ml	23 (57.5%)
≥400 ng/ml	17 (42.5%)
Child–Pugh Class	
A	19 (47.5%)
B	21 (52.5%)
ECOG PS	
0~1	23 (57.5%)
2	17 (42.5%)
Systematic treatment	
None	25 (62.5%)
Yes	15 (37.5%)
TACE	
None	24 (60%)
Yes	16 (40%)

Systematic treatment: targeted therapy or immune checkpoint inhibitor therapy.
AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transarterial chemoembolization.

of the target artery was not routinely used because of the concern that it may cause ischemic necrosis to the liver tissue. A total of 14 cases received TACE only once, and repeat TACE was performed in only two patients. A total of 15 cases received concurrent systematic therapies, including seven cases with sorafenib, three cases with Lenvatinib, and five cases with camrelizumab plus apatinib. Two patients took the target drug less than 1 month due to deterioration of liver function and gastrointestinal bleeding.

I-125 seed strand implantation

The success rate of the operation was 100%. A total of 43 I-125 seed strands were implanted for the treatment of 40 HCC patients with extensive PVTT. A total of 37 patients received single I-125 seed strand, and three patients received double I-125 seed strands through the bilateral portal vein approach (Figure 2). The average number of I-125 seeds implanted was 28 ± 10 seeds. Single-photon emission CT (SPECT)/CT images showed a distribution of I-125 seeds that surrounded the tumor thrombosis (Figure 3).

Overall survival

By the end of the follow-up period (median 3.5, interquartile range (IQR), 2~8.5), 39 patients had died. The median OS of the entire patient population was 92 days in this study (95% confidence interval (CI): 77~108 days). The median OS was 128 days (95% CI: 101~155 days) for the I-125 seed strand plus systematic treatment group and 75 days (95% CI: 36~114 days) for the I-125 seed strand alone group (log-rank test, $p = 0.037$) (Figure 4). Of the 39 deaths during follow-up, nine patients died of gastrointestinal bleeding, and 30 patients died of liver failure. Of those nine patients who died of gastrointestinal bleeding, six patients received I-125 seed strand implantation alone, while three patients were treated with I-125 seed strand combined with systematic treatment (Fisher's test, $p = 1.000$).

Multi-variable analyses

The present univariate analysis results revealed that tumor burden of more than 50%, Child–Pugh grade B, and I-125 seed strand implantation alone were risk factors for poor prognosis for HCC with extensive PVTT. The multivariate Cox regression analysis demonstrated that I-125 seed strand implantation combined with systematic treatment was related to a better prognosis (Table 2).

Safety evaluation

No serious complications related to I-125 seed strand implantation, such as intraperitoneal hemorrhage or displacement of I-125 seeds, were recorded in this study. One patient developed a fever after I-125 seed strand implantation and improved with symptomatic treatment. No radiation hepatitis and gastroenteritis symptoms, such as decreased appetite, vomiting, and diarrhea, were observed. There were no statistically significant differences between pre- and postoperative white blood cell (WBC), platelet (PLT), hemoglobin (HB), red blood cell (RBC), total bilirubin (TB), alanine

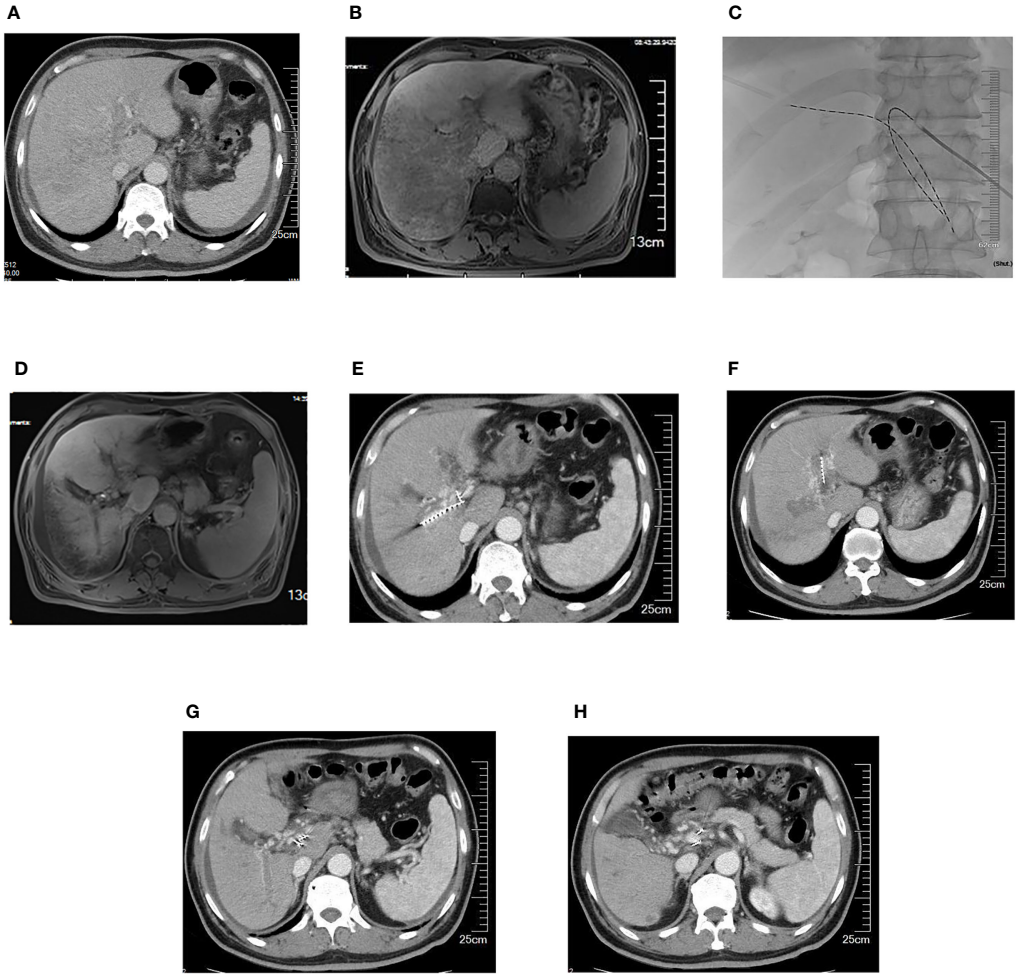

FIGURE 2
A 63-year-old male patient with HCC and extensive portal vein tumor thrombus. **(A)** Portal vein obstruction by the thrombus in bilateral portal branches and major portal vein. **(B)** Portal vein blood perfusion defect in the right liver lobe. **(C)** Two iodine-125 seed strands implanted via bilateral portal vein approach. **(D)** Portal vein blood perfusion of the right liver lobe increased. **(E–H)** Five months later, iodine-125 seed strands were still fixed in the thrombus, while the thrombus partially shrank and collateral circulation around portal vein increased. HCC, hepatocellular carcinoma.

aminotransferase (ALT), and prothrombin time (PT) levels ($p > 0.05$). Aspartate aminotransferase (AST) on the fifth day after the operation was lower ($p < 0.05$). Grade 1–2 hand–foot syndrome occurred in five cases (3/15, 20%) and Grade 1 hypertension in two patients (13%) in the combination group. Gastrointestinal bleeding was observed in 12 cases: six cases (6/25) in the I-125 seed strand alone group and six cases (6/15) in combination with the systematic treatment group. Among six cases with gastrointestinal bleeding in the patient combination group, three cases presented positive stool occult blood tests and recovered normally without blocking systematic treatment.

Discussion

This study shows that I-125 seed strand implantation is a safe and effective local treatment method for extensive PVTT in HCC patients. There was no active treatment of intrahepatic parts of HCC. The median OS of all patients was 92 days (95% CI: 77~108). The combination of systematic treatment and I-125 seed strand implantation can prolong the survival time when compared with I-125 seed strand implantation alone at 128 days (95% CI: 101~155 days) and 75 days (95% CI: 36~114 days), respectively ($p = 0.037$). Multivariate analysis demonstrated that I-125 seed strand implantation combined with systematic treatment was related to a better prognosis.

A retrospective study based on 484 HCC with different types of PVTT demonstrated that the extent of PVTT was closely related to prognosis. The median survival time of Vp1 to Vp4 was 14.6, 9.4, 5.8, and 4.8 months, respectively (3). Sorafenib alone has not been reported to significantly prolong the survival time of Vp4 PVTT with a median survival time of 3.2 months in a single-arm retrospective study by Jeong (14). Systemic treatment and a combination with locoregional therapies, such as radiation therapy, hepatic arterial infusion chemotherapy (HAIC), TACE, and Y90 transarterial radioembolization (Y90 RE), were recommended for unresectable HCC patients with PVTT, especially in Asian patients (4, 5, 15, 16). Recently, in a

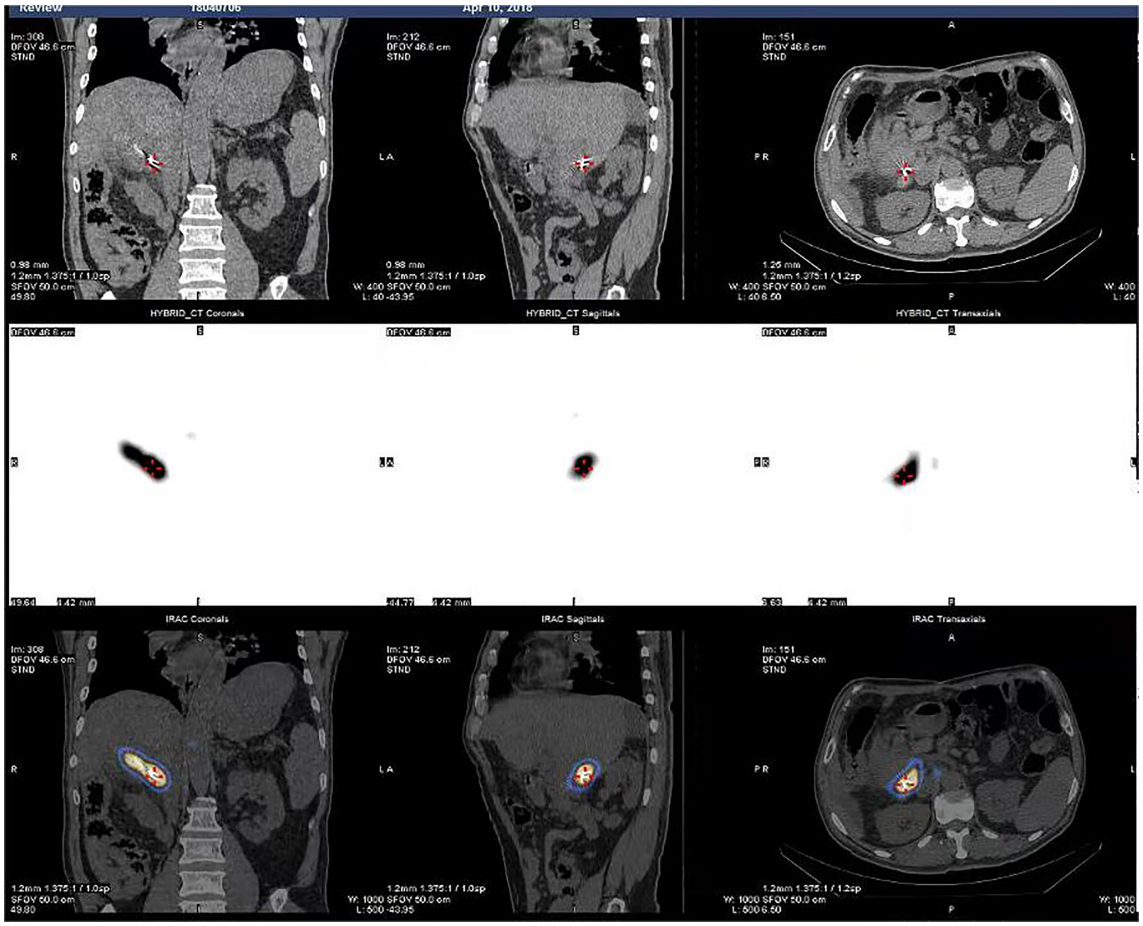

FIGURE 3
SPECTCT images showed dose distribution of I-125 seeds that surrounded the tumor thrombosis.

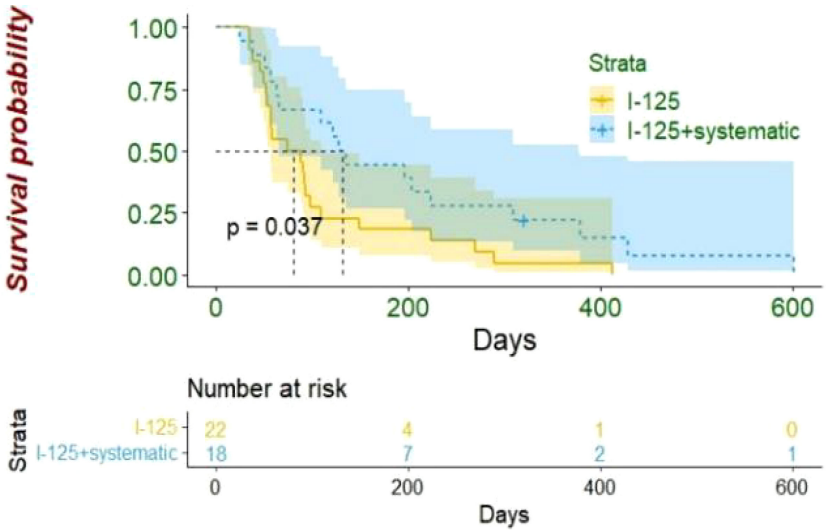

FIGURE 4
In HCC patients with extensive portal vein tumor thrombus, the median OS was better in I-125 seed strand plus systematic treatment group than I-125 seed strand alone group (128 vs. 75 days, p = 0.037). HCC, hepatocellular carcinoma; OS, overall survival.

TABLE 2 Univariate and multivariate analyses for patients treated with I-125 seed strand.

Variable	Univariate analysis			Multivariate analysis		
	HR	*p*	95% CI	HR	*p*	95% CI
Age						
≤65	1					
>65	1.080	0.832	0.531~2.195			
Location of tumor						
Single liver lobe	1					
Whole liver lobe	0.956	0.890	0.502~1.819			
Cirrhosis						
None	1					
Yes	1.566	0.194	0.796~3.082			
Tumor type						
Infiltrative	1					
Nodular	1.247	0.540	0.616~2.526			
Tumor burden						
<50%	1			1		
≥50%	2.037	0.034	1.056~3.928	1.935	0.101	0.879~4.259
AFP						
<400 ng/ml	1					
≥400 ng/ml	0.783	0.463	0.408~1.504			
Extra-hepatic disease						
None	1					
Yes	1.417	0.412	0.616~3.259			
Child–Pugh class						
A	1			1		
B	2.005	0.045	1.015~3.959	1.412	0.436	0.593~3.363
ECOG PS						
≤1	1					
>1	0.862	0.663	0.441~1.683			
TACE						
None	1			1		
Yes	0.564	0.115	0.276~1.150	0.631	0.249	0.289~1.379
Systematic treatment						
None	1			1		
Yes	0.495	0.040	0.253~0.969	0.410	0.014	0.201~0.839

AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; TACE, transarterial chemoembolization.

randomized controlled trial (RCT), Zheng et al. (17) compared sorafenib plus HAIC (n = 32) and sorafenib alone (n = 32) for advanced HCC with major PVTT (Vp3 and Vp4). The median OS was superior in the sorafenib plus HAIC group than the sorafenib alone group (16.3 *vs.* 6.5 months, $p < 0.001$). HAIC was an alternative or integrative method for HCC patients with PVTT, especially for Vp3–Vp4. In a propensity score-matching retrospective cohort study, Kim et al. (18) evaluated the efficacy of liver-directed concurrent chemoradiotherapy (LD-CCRT) (n = 52) compared with sorafenib (n = 27) in HCC patients with PVTT.

After propensity score matching, the median overall survival (OS) was 4.3 and 9.8 months in the sorafenib and LD-CCRT groups, respectively ($p = 0.002$). A significant survival benefit was observed for PVTT type III and IV HCC patients in the LD-CCRT group than the sorafenib group, with 1-year of OS 41.3% *vs.* 14.3% ($p = 0.027$) and 54.5% *vs.* 0% ($p = 0.038$), respectively. In the three RCTs (SARAH, SIRveNIB, and SORAMIC) (19–21), these results showed that Y90 RE was not inferior to sorafenib for advanced HCC. Y90 RE is an effective and alternative method for advanced HCC. According to the 2021 National Comprehensive Cancer Network (NCCN) guidelines, TARE is more suitable for HCC patients with segmental or lobar PVTT (22).

The 75-day median OS of the I-125 seed strand alone group in this study was comparable to 2.7~4 months of natural median OS in HCC patients with PVTT (7, 23, 24). The survival outcomes in the combination of systematic treatment and I-125 seed strand implantation group were also worse than those in the Zheng et al. study (17) and SARAH, SIRveNIB, and SORAMIC trials (19–21). There could be several reasons for this. In this study, there was no active treatment for intrahepatic parts of HCC. The majority of the patients in this study did not receive locoregional treatments for intrahepatic tumors after iodine-125 strand implantation, such as TACE (60%), HAIC (0%), and Y90 RE (0%), and systemic treatment (62.5%). Standard TACE with lipiodol plus gelatin sponge embolization was not routinely used, which led to a less therapeutic effect for intrahepatic HCC. Repeat TACE procedures were few. Moreover, compared to the patients in those studies, the majority of the patients included in our study were relatively more late-staged with tumor burden exceeding 50% of the liver volume (52.5%). Moreover, we included patients who were not eligible for irradiation stent placement (25), and all included patients in this study with bilateral first portal branches had complete occlusion and major portal vein invasion. The more tumor thrombus burden and worse insufficient portal vein blood flow perfusion may lead to a bad prognosis (2).

Reports on the treatment of PVTT with endovascular brachytherapy using I-125 seeds are increasing gradually (26, 27). As the irregular morphology of PVTT, deep location, and the surrounding important tissues and organs are dense, improper radiation dose would lead to adjacent organ damage. Compared with external radiation therapy, brachytherapy using I-125 seed implantation has the highest local dose and more conformal dose distribution for PVTT. Hu et al. (27) conducted a retrospective study to evaluate the safety and efficacy of TACE combined with CT-guided iodine-125 implantation in HCC with the first branch of PVTT. The results demonstrated that I-125 seed implantation combined with TACE prolonged significantly the survival time compared to TACE alone (11.3 *vs.* 6 months, $p < 0.01$) and increased the local control rate of PVTT (78% *vs.* 18%, $p < 0.01$). Wang et al. (28) reported that I-125 seed strand combined with TACE can be a safe and feasible treatment option for HCC with Vp4. Compared with TACE monotherapy, the combined therapy can significantly improve the median survival (9.8 *vs.* 5.2 months, $p = 0.024$). Our center has reported that portal vein irradiation stent was a safe and effective method for the treatment of HCC with major portal vein tumor thrombus (8, 9, 25). However, stents cannot be implanted effectively into the portal vein for HCC patients with extensive PVTT in this study. Therefore, I-125 seed strand was implanted in HCC patients with extensive PVTT who were unsuitable for portal vein irradiation stent in our center. The advantages of I-125 seed strand are as follows: 1) good conformability with tumor thrombus can lead to an even and complete radioactive dose coverage, 2) I-125 seed strand is not easy to displace after implantation due to the portal vein fully filled by tumor thrombus, 3) I-125 seeds can inhibit the growth of tumor thrombus and even recover partially blood flow of intrahepatic portal vein, and 4) I-125 seed strand can prevent and delay the time of the established collateral circulation around the portal vein blocked again by the tumor thrombus, which is important for the safety of TACE or HAIC. Intrahepatic portal vein perfusion cannot be improved immediately after I-125 seed strand implantation. TACE treatment is considered only for HCC with extensive PVTT with adequate collateral circulation around the occluded portal vein and good liver function in this study. Both univariate and multivariate analyses revealed that systematic treatment was an independent risk factor affecting the prognosis of this group of patients. A study has shown that targeted therapy drugs and immune checkpoint inhibitors may have synergistic sensitization effects with I-125 seeds (29). However, excitably, although this study has poor baseline characteristics, compared with I-125 seed strand implantation alone, I-125 seed strand plus systematic treatment showed a better OS in this study. No serious complications were observed in this study. I-125 seed strand combined with systematic treatment did not increase the risk of death from gastrointestinal bleeding.

There were several limitations to this study. First, the sample size is small, and it is a single-arm retrospective study. Due to the fact that the majority of the patients in this study received single I-125 seed strand implantation, further research is needed to determine whether double I-125 seed strands are more effective. Second, as the last stage of PVTT and more tumor thrombus burden, it is difficult to fully and accurately compare this study with previous studies. A triple combination of HAIC and I-125 seed strand and systematic treatment may be a better choice for HCC patients with extensive PVTT. Third, the evaluation of tumor thrombus response was abandoned given the lack of well-recognized criteria for measuring the portal vein tumor on CT or MRI images. A larger sample of prospective randomized controlled studies should be carried out to confirm the safety and effectiveness of I-125 seed strand implantation in HCC patients with extensive PVTT.

Conclusions

The study shows that endovascular brachytherapy with I-125 seed strand implantation is a safe and effective treatment method for extensive PVTT in HCC patients. As compared to I-125 seed strand alone, the combination of systematic treatment and I-125 seed strand implantation can prolong the survival time in HCC patients with extensive PVTT.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

This study was reviewed and approved by the ethic committee of the Affiliated Hospital of Jiangsu University (KY2023K0604). Written informed consent was waived due to its retrospective nature. All methods were carried out in accordance with declaration of Helsinki.

Author contributions

ZT and DW: methodology, software, investigation, formal analysis, and writing–original draft. JG: technological guidance. HW: data curation and review. JZ: resources and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Efficacy and safety of transarterial chemoembolization combined with lenvatinib and camrelizumab in patients with BCLC-defined stage C hepatocellular carcinoma

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Objective: To investigate the effectiveness and safety of combining transarterial chemoembolization (TACE) with lenvatinib and camrelizumab in patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC).

Methods: We retrospectively analyzed 141 patients with BCLC stage C HCC: 57 were treated with TACE combined with lenvatinib plus camrelizumab (T + L + C), 41 were treated with TACE combined with camrelizumab (T + C), and 43 were treated with TACE (TACE). The primary outcomes were overall survival (OS) and progression-free survival (PFS), and the secondary outcomes were the objective response rate (ORR) and adverse events (AEs). Factors that affected survival were identified via Cox regression analysis.

Results: Comparison of the three groups revealed a significant difference in the median overall survival (mOS), 19.8 months (95% CI 15.7–23.9) in the T + L + C combined group vs 15.7 (95% CI 13.1–18.3) months in the T + C combined group vs 9.4 (95% CI 6.2–12.5) months in the TACE group ($P < 0.001$). The median progression-free survival (mPFS) was significantly better in the T + L + C combination group than in the T + C combination group and the TACE group [11.4 (95% CI 7.6–15.3) months vs 8.4 (95% CI 6.2–10.5) months vs 4.8 (95% CI 3.2–6.3) months, respectively, $P < 0.001$)]. The objective response rate (ORR) (57.9%) and the disease control rate (DCR) (75.4%) patients in the combined T + L + C group were higher than those in the other two groups. More patients in the combined T + L + C group experienced AEs, with 16 (28.1%) patients experiencing AEs of grade 3 or higher.

Conclusions: In patients with BCLC stage C HCC, those receiving the T + L + C combination demonstrated a superior survival benefit and acceptable safety profile compared patients receiving either TACE or the T + C combination.

KEYWORDS

hepatocellular carcinoma, transarterial chemoembolization, lenvatinib, camrelizumab, efficacy

Introduction

According to recent statistics, primary liver cancer has become the sixth most prevalent type of cancer globally and is responsible for the third-highest number of cancer-related deaths. The most common type of primary liver cancer is hepatocellular carcinoma (HCC), which accounts for 75–85% of cases (1). Due to the insidious onset of HCC, less than 30% of patients are eligible for radical treatment at the initial diagnosis. Unfortunately, treatment options are limited for those diagnosed with advanced-stage HCC. However, transarterial chemoembolization (TACE) is a commonly used non-surgical treatment for intermediate to advanced HCC. TACE is effective in controlling tumor growth by increasing drug concentrations locally (2, 3). However, the possibility of tumor recurrence and metastasis in advanced HCC treated with TACE alone is high. TACE causes hypoxia-induced up-regulation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF) in tumors and maximizing tumor ischemic necrosis (4, 5). In particular, increased expression of VEGF is strongly associated with a poor prognosis of cancer (6, 7). Lenvatinib is an oral multikinase inhibitor that targets the inhibition of the expression of VEGF receptor 1-3 isoforms, FGF receptor 1-4 isoforms, platelet growth factor receptor α, RET, and KIT expression (8, 9), resulting in the inhibition of local tumor angiogenesis. In phase III studies, nivolumab and pembrolizumab showed promising clinical efficacy as first- and second-line treatments for advanced HCC, respectively, but neither met the prespecified endpoints (10, 11). Compared to limited immune checkpoint inhibitor (ICI) monotherapy for advanced HCC, ICI combined with TACE therapy delayed tumor progression and allowed downgrading of disease with access to surgical resection (12, 13). The encouraging results of the IMbrave150 trial showed that atezolizumab (anti-programmed death ligand 1) and bevacizumab (anti-VEGF) reduced the risk of disease progression by 34% and prolonged the median survival time in patients with unresectable HCC compared to sorafenib (14), and also support the synergistic antitumor effects of antiangiogenic combination immunotherapy. However, due to resistance to systemic therapy, most patients with advanced HCC do not achieve long-term survival benefits (15). Considering the synergistic anti-cancer effects of TACE combined with lenvatinib and programmed death 1 (PD-1) inhibitors, we conducted this retrospective cohort study to evaluate the efficacy and safety of T + L + C combination therapy versus T + C combination therapy and TACE alone in patients with BCLC stage C HCC.

Materials and methods

Patients and study design

From January 2020 to November 2021, we conducted a retrospective study of consecutive HCC patients with BCLC stage C admitted to our institution. Patients included in the study met the following criteria: age ≥18 years and ≤75 years; patients with a clear diagnosis of unresectable HCC (BCLC stage C); at least one measurable lesion as defined by the Modified Response Evaluation Criteria for Solid Tumors (mRECIST); Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 1 to 2; and adequate organ function with Child-Pugh classification of A or B. The following exclusion criteria were applied: patients who received lenvatinib for less than 4 weeks; patients who had undergone surgical resection or other local treatments such as radiotherapy, ablation, HAIC; patients with other primary malignancies or severe dysfunction of vital organs such as heart, brain, kidney and lung; patients with a history of organ transplantation and bone marrow suppression; and patients with incomplete data or failed follow-up.

TACE procedure

A catheter was inserted through the femoral artery using the Seldinger technique, and the phrenic, common hepatic, and superior mesenteric arteries were selected for imaging to assess the blood supply to the tumor. When staining of the tumor lesions was seen, the tumor blood supply vessels were super-selected with a microcatheter, and the intrahepatic lesions were embolized using super-liquefied iodized oil, lobaplatin, and raltitrexed. Conventional TACE (cTACE) was supplemented with embolization using gelatin sponge particles or blank microspheres, whereas drug-eluting bead-based TACE (DEB-TACE) was performed using CalliSpheres-carrying microspheres loaded with injections of piroxicam hydrochloride, which were slowly injected at a rate of 1 mL/minute to embolize intrahepatic lesions until blood flow to the tumor vasculature was interrupted. Post-TACE evaluation and follow-up were performed every 4–8 weeks, and TACE was repeated as needed if residual active lesions remained in the tumor, while the hepatic function scores were maintained at a Child-Pugh classification A or B.

Lenvatinib and camrelizumab

The day after the first TACE procedure, patients received an intravenous infusion of 200 mg camrelizumab, which was administered every 3 weeks. Lenvatinib was administered orally at 8 mg/day (weight < 60 kg) and 12 mg/day (weight ≥ 60 kg). Patients with Child-Pugh classification B received 8 mg daily, regardless of weight. In the event of lenvatinib-related toxicity, the dose was reduced for symptomatic relief [4 mg/day (weight < 60 kg) and 8 mg/day (weight ≥ 60 kg)]. According to the dosing guidelines, when adverse events (AEs) of grade ≥3 occurred, patients received a reduced dosage of the drug or discontinued therapy until symptoms resolved or were downgraded to grade 1 or 2.

Follow-up and evaluation

The follow-up cut-off date of this study was December 31, 2022. Clinical information was retrieved through the medical record system, and all patients underwent tumor marker testing and hematologic and biochemical testing, including blood routine, coagulation index, liver and kidney function, serum ions, and thyroid function evaluation every 4–8 weeks to assess AEs. Enhanced computed tomography (CT) or magnetic resonance

imaging (MRI) was performed every 2 months, and whenever residual tumors or new lesions were confirmed. Treatment was administered according to the patient's liver function, general condition, and tumor status. The primary outcomes of this study were OS and PFS. OS was defined as the time from the first TACE procedure to death from any cause. PFS was defined as the time from the first TACE procedure to progression or death from any cause. Secondary outcomes were objective response rate (ORR) and disease control rate (DCR) as assessed according to mRECIST criteria. Safety was assessed according to version 5.0 of the National Cancer Institute Common Terminology Criteria.

Data analysis

Data from all patients were analyzed using IBM SPSS Statistics v.25.0 software. Categorical data were expressed as frequencies, and quantitative data were expressed as mean ± standard deviation and median (interquartile spacing) of normally and skewed distributed variables, respectively. Categorical data were compared between the three groups using the $\chi 2$ test or Fisher's exact test, as appropriate. Quantitative data were compared using a multi-sample nonparametric (Kruskal–Walls rank sum test) test. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. Cox risk proportional models were used for univariate and multifactorial analyses to detect independent influences on OS and PFS. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients

The flow chart of this study is shown in Figure 1. Patients diagnosed with BCLC stage C HCC between January 2020 and November 2021 at the Affiliated Cancer Hospital of Harbin Medical University were screened for eligibility, and finally, 141 patients were included in the study (57 in the T + L + C group, 41 in the T + C group, and 43 in the TACE group). Table 1 summarizes the baseline demographic and clinical characteristics of all patients, with the highest percentage of patients with portal vein invasion in the TACE group (69.8%) and the lowest percentage of patients with portal vein invasion in the T + C group (51.2%). Among patients with extrahepatic metastases, the highest proportion of patients in the T + L + C group had extrahepatic metastases (40.4%) and the lowest proportion in the TACE group (25.6%). There were no significant differences between the three groups in terms of demographic, clinical, or tumor characteristics. Our statistical analysis of the choice and number of TACE, the dose of iodinated oil for the first TACE, the type and dosage of chemotherapeutic drugs, and the preoperative liver function indices of the three groups showed that there were statistically significant differences between the three groups in terms of the number of TACE procedures, the dose of iodinated oil, and the dosage of lobaplatin ($P < 0.05$), while there were no significant differences in the preoperative liver function indexes between the three groups. Patients in the T + L + C group underwent a total of 224 TACE procedures with a median of 4 and a mean interval of 78.3 (55.5, 124.1) days between TACE sessions; patients in the T + C group underwent a total of 166 TACE procedures with a median of 4 and a mean interval of 70.2 (50.4, 99.3) days between TACE sessions; and patients in the TACE group underwent a total of 137 procedures with a median of 3 and a mean interval of 62.0 (45.0, 81.7) days between TACE sessions. There was a significant difference between the groups in the number of TACE procedures and the mean number of days between the TACE sessions ($P = 0.034$) (Supplementary Table 1).

Overall survival

The entire cohort was followed for 1.3 to 31.9 months, with a median follow-up time of 14.0 months. During the follow-up period, 29 cases (50.9%) in the T + L + C group, 30 cases (73.2%) in the T + C group, and

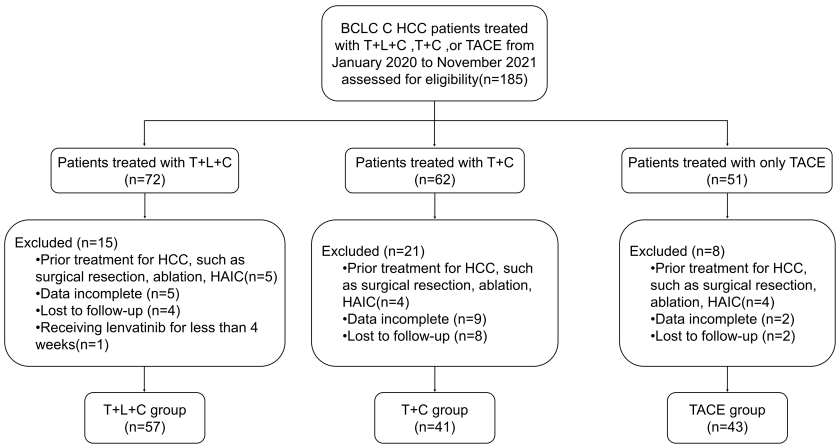

FIGURE 1
Flowchart of the patient selection process. HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; T+L+C, transarterial chemoembolization combined with lenvatinib plus camrelizumab; T+C, transarterial chemoembolization combined with camrelizumab; TACE, transarterial chemoembolization.

TABLE 1 Baseline characteristics of the patients.

Characteristic	T+C (n=41)	T+L+C (n=57)	T (n=43)	P value
Age	55.27±10.48	53.18±9.25	53.5±9.35	0.552
Sex				0.326
Male	34 (82.9%)	49 (86.0%)	32 (74.4%)	
Female	7 (17.1%)	8 (14.0%)	11 (25.6%)	
Etiology				0.808
Hepatitis B	30 (73.2%)	44 (77.2%)	34 (79.1%)	
Others	11 (26.8%)	13 (22.8%)	9 (20.9%)	
Cirrhosis				0.929
Yes	30 (73.2%)	43 (75.4%)	33 (76.7%)	
No	11 (26.8%)	14 (24.6%)	10 (23.3%)	
ECOG PS score				0.269
1	24 (58.5%)	40 (70.2%)	32 (74.4%)	
2	17 (41.5%)	17 (29.8%)	11 (25.6%)	
Child-Pugh class				0.911
A	36 (87.8%)	52 (91.2%)	39 (90.7%)	
B	5 (12.2%)	5 (8.8%)	4 (9.3%)	
ALBI Grade				0.737
1	19 (46.3%)	25 (43.9%)	19 (44.2%)	
2	20 (48.8%)	31 (54.4%)	24 (55.8%)	
3	2(4.9%)	1 (1.8%)	0 (0.0%)	
Number of tumors				0.215
1	21 (51.2%)	33 (57.9%)	27 (62.8%)	
2	5 (12.2%)	4 (7.0%)	0 (0.0%)	
3	15 (36.6%)	20 (35.1%)	16 (37.2%)	
Largest tumor size (mm)	95 (59,110)	82 (50,111)	82 (57,98)	0.430
portal vein invasion				0.219
Yes	21 (51.2%)	35 (61.4%)	30 (69.8%)	
No	20 (48.8%)	22 (38.6%)	13 (30.2%)	
Extrahepatic metastasis				0.304
Yes	14 (34.1%)	23 (40.4%)	11 (25.6%)	
No	27 (65.9%)	34 (59.6%)	32 (74.4%)	
AFP level (μg/L)				0.133
≤400	24 (58.5%)	25 (43.9%)	16 (37.2%)	
>400	17 (41.5%)	32 (56.1%)	27 (62.8%)	

Data are presented as mean ± standard deviation or n (%) or median (25th-75th), T+L+C, transarterial chemoembolization combined with lenvatinib plus camrelizumab; T+C, transarterial chemoembolization combined with camrelizumab; TACE, transarterial chemoembolization; ECOG-PS, Eastern Cooperative Oncology Group performance status; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein.

43 cases (100.0%) in the TACE group had a mortality outcome. The median OS (mOS) was 19.8 months (95% CI 15.7–23.9 months) in the T + L + C group, 15.7 months (95% CI 13.1–18.3 months) in the T + C group, and 9.4 months (95% CI 13.1–18.3 months) in the TACE group ($P < 0.001$; Figure 2). The median PFS (mPFS) was 12.7 months (95% CI 7.6–17.8 months) in the T + L + C group, 9.1 months (95% CI 5.3–12.9 months) in the T + C group, and 4.8 months (95% CI 5.3–12.9 months) with TACE alone ($P < 0.001$ Figure 3).

Analysis of prognostic factors

The ORR and DCR in the T + L + C group (ORR: 57.6%; DCR: 75.4%) were higher than in the T + C group (ORR: 41.5%; DCR: 58.5%) and the TACE group (ORR. 32.6%; DCR: 55.8%). There were no significant differences in the ORR and DCR between the T + L + C combination group and the T + C combination group ($P > 0.05$), whereas the differences in the ORR and DCR between the T + L + C combination group and the TACE group were statistically significant ($P < 0.05$) (Table 2). According to the results of the univariate and multivariate analyses (Table 3), the combination of T + L + C significantly improved PFS (HR,0.57; 95% CI,0.46–0.71; $P < 0.001$), in addition, patients with portal vein invasion had significantly shorter PFS (HR, 2.46; 95% CI,1.67–3.62; $P < 0.001$). Similarly, multivariate analysis of OS determined that T + L + C combination therapy significantly prolonged OS in patients (HR, 0.49; 95% CI, 0.39–0.62; $P < 0.001$), while the presence of portal vein invasion contributed negatively to OS in patients (HR, 2.54; 95% CI, 1.63–3.94; $P < 0.001$), whereas the treatment option and the presence of portal vein invasion were identified as independent prognostic factors for OS and PFS. The ECOG PS score, Child-Pugh classification, ALBI grade, extrahepatic metastasis, tumor number, largest tumor size, and AFP level were not significantly correlated with OS and PFS. Subgroup analysis of OS factors showed that compared to the T + C combination therapy group, OS did not differ significantly in outcomes across all subgroups, although T + L + C combination therapy achieved a longer OS in patients with portal vein invasion, extrahepatic metastasis, Child-Pugh classification A, ALBI grade 2/3, with cirrhosis, male sex, and age ≤55 years (Figure 4).

Subsequent treatment after progression

Before the follow-up cut-off point, 35 cases in the combined T + L + C group showed disease progression, 26 patients required further treatment, and 7 patients chose supportive treatment; 34 cases in the combined T + C group showed disease progression, 25 patients required further treatment, and 7 patients selected supportive treatment; 38 cases in the TACE group showed disease progression, 26 patients took further treatment, and 6 patients chose supportive treatment. Due to limited treatment options after the progression of advanced HCC, some patients in three groups chose to abandon treatment (Supplementary Table 2).

Safety results

The most common treatment-related AEs of any grade in patients in the T + L + C group were elevated total bilirubin (TB) (70.2%), fatigue (50.9%), hypertension (47.4%), weight loss (42.1%), thrombocytopenia (42.1%), and elevated aspartate aminotransferase (AST) (40.4%). Two patients in the T + L + C group had serious treatment-related emergency AEs, including one case of cerebral hemorrhage and one case of immune-related pneumonia, and no emergency adverse events (AEs) occurred in the other two groups (Supplementary Table 1). Dose reduction or interruption occurred in 16 (28.1%) and 11 (26.8%) patients in the T + L + C and T + C groups, respectively. We performed statistical analysis of biochemical indicators of liver function for the final recovery of the three groups of patients before the follow-up deadline, and only the laboratory indicator alanine

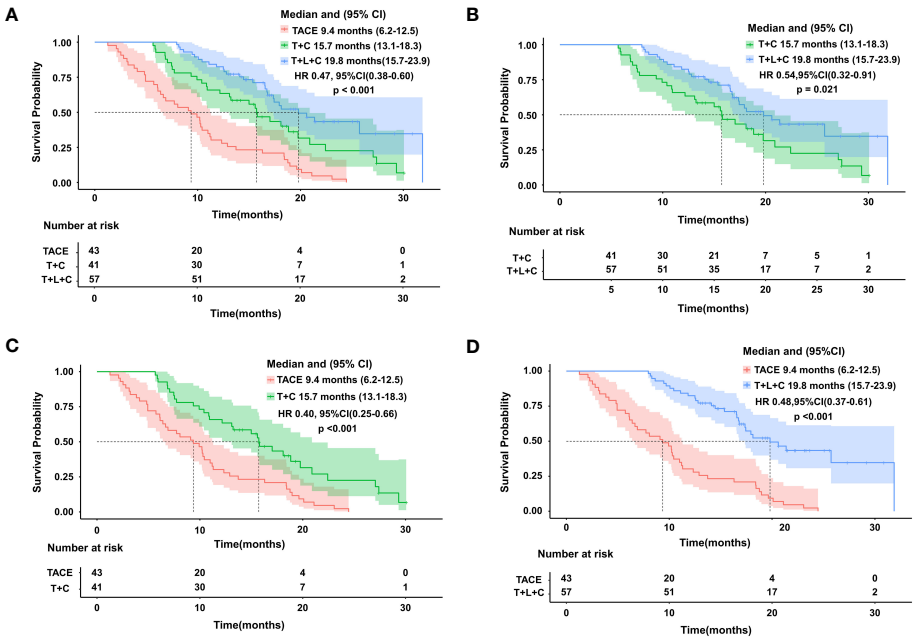

FIGURE 2
Kaplan-Meier survival curves showing OS according to treatment.Comparison of OS among the three groups **(A)**. OS comparison between T+L+C group and T+C group **(B)**. OS comparison between TACE group and T+C group **(C)**. OS comparison between T+L+C group and TACE group **(D)**.

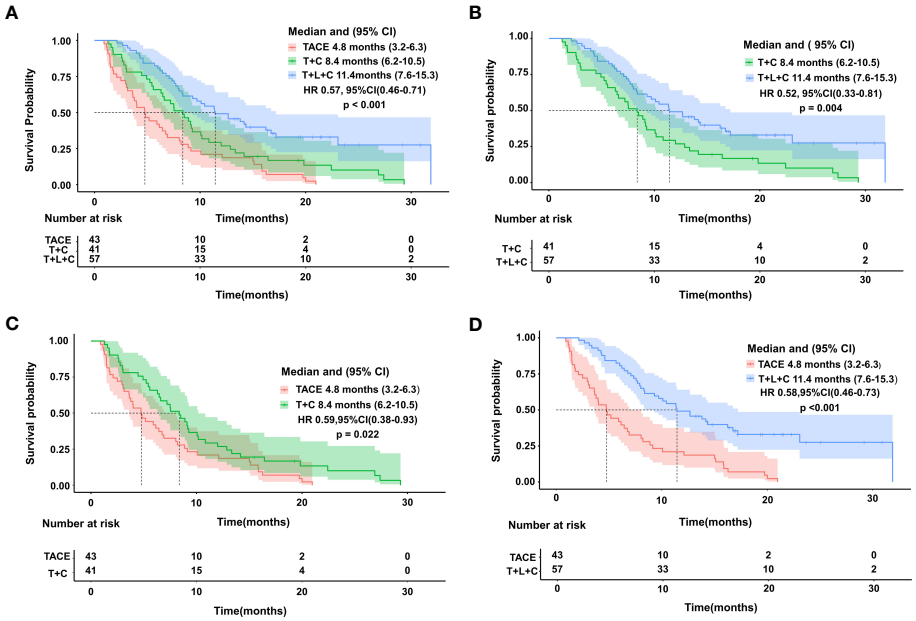

FIGURE 3
Kaplan-Meier survival curves showing PFS according to treatment.Comparison of PFS among the three groups **(A)**. PFS comparison between T+L+C group and T+C group **(B)**. PFS comparison between TACE group and T+C group **(C)**. PFS comparison between T+L+C group and TACE group **(D)**.

aminotransferase (ALT) showed statistically significant differences between the groups (P = 0.014), while the remaining indicators AST, TB and ALB did not show statistically significant differences between the groups (P > 0.05), as shown in Table 4.

Discussion

The results showed that patients treated with the T + L + C combination achieved longer OS and PFS compared to treatments with the T + C combination and TACE monotherapy. The T + L + C combination group also showed a better tumor response rate. We did not observe a significant difference in ORR and DCR between the T + L + C combination treatment and the T + C combination, but patients receiving the T + L + C combination achieved a better tumor response and longer survival, due to the long-term survival benefits provided by lenvatinib. We observed by further subgroup analysis that T + L + C combination therapy reduced the risk of death in the subgroup with portal vein invasion, extrahepatic metastasis, Child-Pugh classification A and cirrhosis.

The hepatic functional reserve is critical to allow patients to adhere to combination therapy to improve prognosis. Previous studies have reported that lenvatinib maintains hepatic functional reserve by slowing the progression of liver fibrosis (16), resulting in a survival benefit for patients with Child-Pugh classification A and cirrhosis. For patients with extrahepatic metastasis and portal vein invasion, our study demonstrated the need for lenvatinib in combination with TACE in addition to PD-1 inhibitors. Multifactorial analysis showed that both T + L + C combination therapy and patients without portal vein invasion were predicted to have better OS and PFS, whereas patients with HCC with portal vein invasion generally had a poor prognosis. One study (17) performed the TACE procedure combined with iodine-125 portal vein particle implantation to achieve a median survival time of 210

TABLE 2 Tumor response according to the mRECIST.

Characteristic	T+C+L vs T+C	P value	T+C+L vs TACE	P value
CR	9(15.8%) vs 3(7.3%)		9(15.8%) vs 1(2.3%)	
PR	24(42.1%) vs 14(34.1%)		24(42.1%) vs 13(30.2%)	
SD	10(17.5%) vs 7(17.1%)		10(17.5%) vs 10(23.3%)	
PD	14(24.6%) vs 17(41.5%)		14(24.6%) vs 19(44.2%)	
ORR	33(57.9%) vs 17(41.5%)	0.108	33(57.9%) vs 14(32.6%)	0.012
DCR	43(75.4%) vs 24(58.5%)	0.076	43(75.4%) vs 24(55.8%)	0.039

Data are presented as n (%). T+L+C, transarterial chemoembolization combined with lenvatinib plus camrelizumab; T+C, transarterial chemoembolization combined with camrelizumab; TACE, transarterial chemoembolization; mRECIST, modified Response Evaluation Criteria In Solid Tumors. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

TABLE 3 Analyses of prognostic factors for survival.

Factor	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value
Treatment option								
T+L+C/T+C/TACE	0.47(0.38-0.60)	<0.001	**0.49(0.39-0.62)**	**<0.001**	0.57(0.46-0.71)	<0.001	**0.59(0.48-0.73)**	**<0.001**
Age	0.99(0.97-1.01)	0.297			1.00(0.98-1.02)	0.751		
Sex								
Female/Male	0.79(0.48-1.29)	0.346			0.66(0.42-1.03)	0.069	0.80(0.50-1.27)	0.342
Etiology								
Hepatitis B/Others	1.31(0.81-2.12)	0.273			1.21(0.78-1.87)	0.392		
Cirrhosis								
Yes/No	1.10(0.70-1.73)	0.687			1.22(0.80-1.86)	0.362		
ECOG PS score								
2/1	0.98(0.65-1.49)	0.929			1.08(0.73-1.58)	0.711		
Child-Pugh class								
B/A	1.26(0.65-2.44)	0.493			1.05(0.56-1.95)	0.889		
ALBI grade								
3/2/1	1.00(0.69-1.45)	0.983			0.97(0.69-1.37)	0.851		
portal vein invasion								
Yes/No	2.62(1.69-4.05)	<0.001	**2.54(1.63-3.94)**	**<0.001**	2.46(1.67-3.62)	<0.001	**2.46(1.67-3.62)**	**<0.001**
Extrahepatic metastasis								
Yes/No	1.07(0.71-1.62)	0.754			1.10(0.76-1.62)	0.610		
Number of tumors								
3/2/1	1.04(0.84-1.27)	0.749			0.98(0.81-1.18)	0.803		
Largest tumor size (cm)								
≥10/<10	1.00(1.00-1.01)	0.425			1.00(1.00-1.01)	0.499		
AFP level (μg/L)								
≥400/<400	1.25(0.84-1.85)	0.278			1.11(0.78-1.60)	0.563		

Analyses were performed using Cox proportional hazard regression model. HR, hazard ratio; CI, confidence interval; T+L+C, transarterial chemoembolization combined with lenvatinib plus camrelizumab; T+C, transarterial chemoembolization combined with camrelizumab; TACE, transarterial chemoembolization; ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein. HR and P values that are meaningful for multivariate analyses are in bold; bold is for eye-catching.

± 17.5 days, whereas Ding et al. (18) combined TACE with lenvatinib to obtain an OS of 14.5 months. Although there are many approaches to the treatment of HCC with portal vein invasion, the best treatment modality has not yet been defined. However, encouragingly, our subgroup data showed that the mOS of patients with portal vein invasion treated with the T + L + C combination reached 16.7 months, which significantly improved the prognosis of these patients. Peng et al. (19) compared TACE in combination with lenvatinib with lenvatinib monotherapy in the treatment of patients with advanced HCC, resulting in a mOS of 17.8 months in the combination group and 11.5 months in the lenvatinib monotherapy group, showing a significant advantage of TACE in combination with lenvatinib in prolonging survival. The results of a meta-analysis involving 8,246 patients showed that TACE combined with tyrosine kinase inhibitors (TKIs) benefited HCC patients in terms of OS and tumor response rate compared to TACE (20).

In addition to combining TACE with lenvatinib, another approach that has been explored by a large number of investigators is the combination of TACE with ICIs. In recent years, some investigators have reported improved tumor response rates with camrelizumab combination for refractory TACE and confirmed a significant advantage of combination therapy over camrelizumab monotherapy (21, 22), which may be related to increased expression of PD-1 and PD-L1 in HCC after TACE, thus enhancing the antitumor activity of immune checkpoint

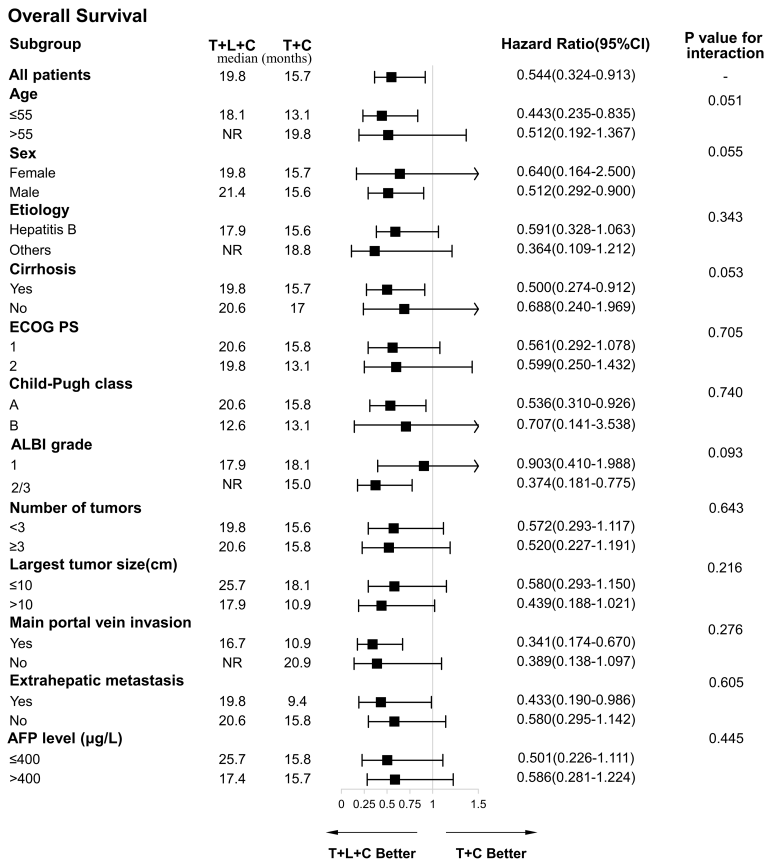

FIGURE 4
Forest plot of the subgroup analyses for overall survival. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ALBI, albumin-bilirubin; AFP, a-fetoprotein; T+L+C, transarterial chemoembolization combined with lenvatinib plus camrelizumab; T+C, transarterial chemoembolization combined with camrelizumab.

inhibitors (23). The results of Brett Marinel et al. (12) also reported an encouraging set of survival data for multimodal immunotherapy with TACE, with a mOS of 35.1 months, a mPFS of 8.8 months, and downgraded disease in four patients, with access to liver transplantation. A multicenter randomized phase 2 trial of patients with advanced HCC treated with camrelizumab monotherapy for follow-up showed an ORR of 14.7% and a 6-month survival rate of 74.4%, demonstrating the antitumor activity and the initial survival benefit of camrelizumab (24). By exploring the two combination approaches, it was determined that both lenvatinib and camrelizumab contributed to the overall outcome of patients with HCC. Li et al. (25) compared lenvatinib in combination with camrelizumab with camrelizumab monotherapy, and the results showed that 1-year survival and PFS were significantly better in the combination group than in monotherapy group because lenvatinib improved the antitumor response to PD-1 inhibitors in addition to anti-angiogenesis. The underlying therapeutic rationale has not been fully elucidated, and it may be that lenvatinib combined with PD-1 inhibitors exert immunomodulatory effects by activating immune pathways, reducing regulatory T (Treg) cell infiltration, inhibiting transforming growth factor β (TGFß) signaling (26), and decreasing the proportion of monocytes and macrophages and increasing the proportion of CD8 + T cells to improve anti-PD-1 efficacy (27). In addition, lenvatinib reactivates interferon-gamma signaling in tumor cells by inhibiting fibroblast growth factor receptor (FGFR) (28) and enhances its combined antitumor activity with anti-PD-1 antibodies by blocking FGFR4 to reduce tumor PD-L1 levels and Treg differentiation (29).

The treatment pattern of TACE combined with lenvatinib and PD-1 inhibitors has been reported (30). A national multicenter retrospective study showed that TACE combined with PD-1 inhibitors and molecular targeted treatments (MTT) had significantly higher OS and PFS than TACE monotherapy (mOS, 19.2 vs. 15.7 months; P = 0.001; mPFS, 9.5 vs. 8.0 months; P = 0.002), with a mOS of 19 months and an ORR of approximately 60%, which were consistent the findings in our study (31). Furthermore, the results of a real-life clinical study showed that patients in the TACE combined with PD-1 inhibitors and the apatinib treatment achieved a mOS of 24.1 months and a mPFS of 13.5 months; this cohort had a better survival outcome than patients in our study, which we considered because the former study included 35.4% of HCC patients with BCLC stage B (32).

It should be noted that triple combination therapy significantly improves the survival outcome of patients with HCC who were in BCLC stage B or BCLC stage C. However,

TABLE 4 Treatment-related adverse events in the three groups.

Adverse events	T+L+C(n=57)		T+C(n=41)		TACE(n=43)	
	All Grade	Grade3/4	All Grade	Grade3/4	All Grade	Grade3/4
Hypertension	27(47.4%)	1(1.8%)	6(14.6%)	0	0	0
fatigue	29(50.9%)	0	15(36.6%)	0	5(11.6%)	0
Nausea	7(12.3%)	0	5(12.2%)	0	5(11.6%)	0
Abdominal pain	13(22.8%)	0	8(19.5%)	0	2(4.7%)	0
Diarrhea	21(36.8%)	0	10(24.4%)	0	2(4.7%)	0
appetite decreased	18(31.6%)	0	12(29.3%)	0	8(18.6%)	0
Rash	16(28.1%)	1(1.8%)	11(26.8%)	0	0	0
Hand-foot syndrome	21(36.8%)	0	3(7.3%)	0	0	0
Mucositis	9(15.8%)	0	4(9.8%)	0	0	0
Hemorrhage	1(1.8%)	1(1.8%)	0	0	0	0
Arthritic pain	2(3.5%)	0	1(2.4%)	0	0	0
Weight loss	24(42.1%)	0	14(34.1%)	0	8(18.6%)	0
Leukopenia	16(28.1%)	1(1.8%)	6(14.6%)	0	6(14.0%)	0
Thrombocytopenia	24(42.1%)	5(8.8%)	11(26.5%)	2(4.9%)	17(39.5%)	0
Elevated TB	40(70.2%)	3(5.3%)	25(61.0%)	5(12.2%)	25(58.1%)	2(4.7%)
Elevated ALT	17(29.8%)	2(3.5%)	16(39.0%)	4(9.8%)	12(27.9%)	0
Elevated AST	23(40.4%)	7(12.3%)	24(58.5%)	4(9.8%)	20(46.5%)	2(4.7%)
Proteinuria	3(5.3%)	1(1.8%)	0	0	0	0
Hypothyroidism	5(8.8%)	0	1(2.4%)	0	0	0
Immune-related pneumonia	1(1.8%)	1(1.8%)	0	0	0	0

Data are presented as n (%). T+L+C, transarterial chemoembolization combined with lenvatinib plus camrelizumab; T+C, transarterial chemoembolization combined with camrelizumab; TACE, transarterial chemoembolization; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

only a few studies have explored the application of triple combination therapy in patients with BCLC stage C HCC. Furthermore, our study was derived from real-life clinical practice. The results of a retrospective study of patients with hepatocellular carcinoma in BCLC stage C achieved mOS and mPFS of 16.9 months and 7.3 months, respectively, in the combined T + L + P group, and mOS and mPFS of 12.1 months and 4.0 month, respectively, in the combined T + L group (33). However, our results showed better survival outcomes than this cohort study, probably because our cohort included patients with a heavier tumor load, a higher proportion of patients with ≥3 tumors, and patients with tumor recurrence. In addition, the subgroup analysis of a previous cohort study showed that the T + L + P combination prolonged OS in patients without portal vein invasion, while our subgroup analysis showed the opposite results, suggesting that patients with portal vein invasion receiving the T + L + P combination had better OS than those receiving the T + P combination (16.7 months vs. 10.9 months, P = 0.001), whereas, in patients without portal vein invasion, there was no significant difference in OS between the two groups (P = 0.115). Due to the small sample size of these two retrospective studies, caution is warranted in interpreting the results of the subgroup analysis.

It is important to highlight the potential toxicity of combination regimens, including hepatic and renal toxicity, in addition to the significantly higher incidence of AEs such as hematological suppression. Additionally, more patients in the combined T + L + C group had hypertension (47.4%) and hand-foot syndrome (36.8%), which is consistent with that observed in previous studies. When counting the interval between TACE sessions, we found that the mean number of days between TACE sessions was lower in the TACE group than in the T + L + C combination group and the T + C combination group, suggesting that the combination therapy required less additional TACE therapy for the same survival period time and therefore the patients had sufficient time to recover liver function. In general, TACE combination drug therapy achieved good antitumor activity and a controlled safety profile.

The limitations of this study include that this was a retrospective study and patient treatment was determined by physician and patient selection, so we could not avoid effects due to selection bias and differences in clinical baseline characteristics on influencing treatment outcomes. Second, this study was conducted in a single institution with a small sample size of patients, and investigator bias and frequency of TACE procedures may have affected the results, which need to be further investigated

in the future with large samples and prospective randomized controlled trials across multiple centers. In conclusion, our study showed that TACE combined with a PD-1 inhibitor and lenvatinib was more effective than TACE combined with a PD-1 inhibitor or TACE treatment alone in patients with stage C BCLC HCC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The requirement of ethical approval was waived by Ethics Committee, Tumor Hospital of Harbin Medical University for the studies involving humans because Ethics Committee, Tumor Hospital of Harbin Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JW, DH, and JZ were involved in the conception and design of the study. JW, HW, and XH provided the provision of study materials or patients. JW, HW, and ZH collected and assembled the data. JW, JZ, and DH were involved in data analysis and interpretation. JW, JZ, HW, and DH were involved in manuscript writing. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1244341/full#supplementary-material

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The impact of liver abscess formation on prognosis of patients with malignant liver tumors after transarterial chemoembolization

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Purpose: Liver abscess is a rare and serious complication after transarterial chemoembolization (TACE) for liver cancer; however, its impact on the prognosis is unclear. This retrospective study examined the outcomes of patients with liver abscess formation following TACE for malignant liver tumors to elucidate the impact of liver abscess formation on the prognosis of these patients.

Methods: From January 2017 to January 2022, 1,387 patients with malignant tumors underwent 3,341 sessions of TACE at our hospital. Clinical characteristics of patients at baseline and follow-up were examined, including treatment and outcome of liver abscess, tumor response to the TACE leading to liver abscess, and overall survival time.

Results: Of 1,387 patients, 15 (1.1%) patients with liver abscess complications after TACE resulted in a total of 16 (0.5%) cases of liver abscess after 3,341 TACE sessions (including one patient with two events). After antibiotic or percutaneous catheter drainage (PCD) treatment, all the infections associated with liver abscesses were controlled. In the PCD group, eight patients died before drainage tube removal, one retained the drainage tube until the end of follow-up, and five underwent drainage tube removal; the mean drainage tube removal time was 149.17 $\pm$ 134.19 days. The efficacy of TACE leading to liver abscess was evaluated as partial response (18.75%), stable disease (37.5%), and progressive disease (43.75%). Eleven patients died during the follow-up period owing to causes unrelated to infections caused by liver abscesses. The survival rates at 3 months, 6 months, 1 year, and 5 years were 86.7%, 50.9%, 25.5%, and 17%, respectively.

Conclusion: Patients with liver abscess formation following TACE for malignant liver tumors experienced prolonged drainage tube removal time after PCD; while this condition did not directly cause death, it indirectly contributed to a poor prognosis in these patients.

KEYWORDS

transarterial chemoembolization, percutaneous drainage, liver abscess, malignant liver tumors, prognosis

Introduction

Transarterial chemoembolization (TACE) is an effective method for the treatment of unresectable malignant liver tumors (1, 2). With the development of embolization concepts and advances in embolization materials, TACE has become the preferred non-surgical treatment for unresectable primary liver cancer and liver metastases (3). It can embolize multiple lesions in a single course of treatment and can be applied repeatedly to the same patient (4).

However, TACE has a series of complications, including post-embolization syndrome (PES), hepatic impairment, and leukopenia, which are common and mild (5). In contrast, a liver abscess is a rare and serious complication. Its incidence is approximately 0.22%–4.46% (5, 6), and it may prolong hospital stay, delay tumor treatment, and even lead to death from severe infection (7–9). The risk factors for liver abscess after TACE include diabetes, biliary abnormalities, large tumor size, and portal vein occlusion (10–13).

Antibiotics combined with percutaneous catheter drainage (PCD) is the mainstream method for the treatment of liver abscess, but there are only a few studies on the therapeutic effect of liver abscess after TACE (8, 9, 12, 13). In addition, the relationship between TACE-induced liver abscess formation and tumor prognosis remains poorly understood. Abscess formation may promote tumor necrosis, but its inflammatory microenvironment may trigger tumor proliferation, migration, and other malignant processes.

Thus, this study aimed to retrospectively examine the outcomes of patients who developed liver abscesses following TACE to elucidate the impact of liver abscess formation on the prognosis of these patients.

Methods

Patients

This study was approved by the ethics committee of our hospital and complies with the principles of the Declaration of Helsinki. Owing to the retrospective nature of this study, the informed consent requirement was waived. The data were anonymized to protect patient privacy. Data were extracted from electronic medical records of patients with malignant liver tumors treated with TACE between January 2017 and January 2022. The characteristics of patients with complicated liver abscesses were reviewed.

The variables of interest included sex, age, comorbidities (e.g., diabetes), tumor status (primary/secondary), tumor diameter, liver function (Child–Pugh class), major surgical history, TACE status (session count, embolic materials used, and session duration), and liver abscess status (clinical symptoms, diagnosis time, and treatment method).

Follow-up assessments included the following variables: liver abscess healed, tumor response, drainage tube removal time, and survival status.

Diagnosis of liver abscess

The diagnostic criteria for liver abscess included contrast-enhanced computed tomography (CT) images showing one or more focal hypodense lesions in the liver that may contain gas and the observation of persistent fever or chills. In addition, one of the following two conditions had to be met: a) blood culture was positive for bacteria; b) aspirated fluid contained a typical purulent substance or was positive for pus culture.

Treatment of liver abscess

In our clinical practice, broad-spectrum antibiotics were applied to patients with suspected liver abscesses after TACE (14). If the infection was not effectively controlled after simple antibiotic treatment, PCD was performed. Infection control was defined as the disappearance of associated clinical symptoms and infection-related indicators returned to normal. The criteria for post-PCD tube removal included the absence of clinical symptoms and a drainage volume of <10 mL/day for three consecutive days and the follow-up CT scan findings showing no evidence of the abscess or <2 cm in size.

Follow-up

All patients with liver abscess formation after TACE were followed up. All patients underwent contrast-enhanced CT/magnetic resonance imaging (MRI) scanning 10–60 days after liver abscess formation to determine liver abscess healed and tumor response. Subsequently, patients were followed up every 2–3 months. Patients who could not visit the hospital were followed up via telephone. Survival was the outcome of interest. If patients developed a second liver abscess, it was recorded as a follow-up endpoint for the first liver abscess. The deadline for the follow-up was December 31, 2022.

Liver abscess healed was defined as infection under control, which no longer needed PCD or intravenous antibiotics. Tumor response represented the therapeutic efficacy of TACE leading to liver abscess formation, which was determined based on contrast-enhanced CT/MRI findings within 1–3 months after TACE using the modified Response Evaluation Criteria in Solid Tumors (15).

Statistical analyses

Data were expressed as means ± standard deviations or percentages. Statistical analysis was performed using SPSS 26.0 (IBM SPSS, Armonk, NY, USA).

Results

A total of 1,387 patients with malignant liver tumors underwent 3,341 TACE sessions at our hospital between January 2017 and

January 2022. Among them, 15 (1.1%) cases were complicated with liver abscess, resulting in a total of 16 (0.5%) liver abscess cases after 3,341 TACE sessions (including one patient with two events) (Figures 1A–C). The patients' baseline characteristics are presented in Table 1.

Eight (50%) TACE sessions were "first" sessions; the mean number of sessions received was 2.31 ± 2.2 (range, 1–9). The mean maximum tumor diameter was 7.09 ± 2.86 (range, 2.8–12.4) cm. Five, one, and 10 TACE sessions were performed using iodized-oil emulsion (IOE), IOE and gelatin sponge particles, and drug-eluting beads (100–300 μm), respectively. The mean TACE duration was 109.06 ± 37.87 (range, 60–180) min. The mean interval from TACE to the diagnosis of liver abscess formation was 14.19 ± 9.21 (range, 3–40) days. The most common symptom was fever (93.8%), followed by chills (43.8%) and abdominal pain (31.3%). One patient received antibiotics only, while 14 patients received PCD combined with antibiotic treatment (Figures 1D, E). The infection caused by liver abscesses was effectively controlled in all patients after treatment. *Enterococcus faecalis* (31.25%) was the most common bacterial species detected in blood/pus cultures (Table 2).

Follow-up assessments after PCD revealed six (40%) abscess cases were healed, nine (60%) abscess cases did not heal completely, eight patients died before drainage tube removal, one patient retained the drainage tube until the end of the follow-up, and five patients underwent drainage tube removal. The mean drainage tube removal time was 149.17 ± 134.19 (range, 73–420) days. A total of zero, three (18.75%), six (37.5%), and seven (43.75%) cases showed complete response (CR), partial response, stable disease, and progressive disease (PD), respectively (Figure 1F). Eleven patients died during the follow-up period owing to causes unrelated to infections caused by liver abscesses (Table 3). The survival rates at 3 months, 6 months, 1 year, and 5 years were 86.7%, 50.9%, 25.5%, and 17%, respectively.

Discussion

PCD is an effective treatment for liver abscess formation after TACE to control infection (13, 16); however, our study showed that its cure rate was low, mainly due to the inability to remove the drainage tube. In addition, the drainage tube removal time in this study was longer than that in patients with community-acquired liver abscesses (17, 18). Delayed or failed extubation may be the result of the connection between abscesses and bile ducts or even biloma formation (19).

One study has argued that complete liquefactive necrosis of tumor lesions may be indicative of a good prognosis and that the discharge of necrotic tumor tissue fluid via the drainage tube may have positive implications for tumor treatment (13). However, the findings of our study were not consistent with previous findings. In this study, no cases were evaluated as CR, while cases with PD accounted for 43.75%. Furthermore, 11 patients died during the follow-up period. The formation of a liver abscess delayed subsequent treatment and was bound to affect the prognosis, although the infection caused by the abscess could be controlled. Liver abscess was not directly related to death, but it led indirectly to poor prognosis in these patients.

History of biliary-enteric anastomosis is an important risk factor for liver abscess formation (6, 9, 10). In this study, 53.3% of the patients had a history of biliary surgery. Some studies have found that Oddi sphincter dysfunction or incision permitted retrograde intestinal bacteria entry into and colonization of the

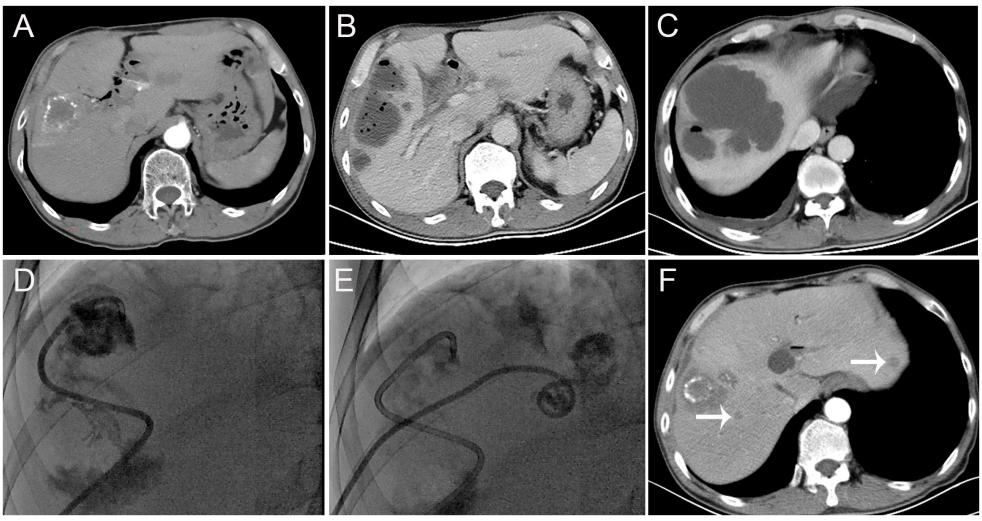

FIGURE 1
Findings from a 62-year-old patient with liver metastasis of cholangiocarcinoma and a history of biliary-enteric anastomosis and one previous transarterial chemoembolization (TACE) session. **(A)** Before the TACE session, contrast-enhanced computed tomography scans revealed hypodense lesions in segment V of the liver, with no significant enhancement. A small amount of iodized-oil emulsion deposit was observed, and the intrahepatic bile duct showed multiple pneumobilia and dilatations. **(B, C)** Thirteen days after this TACE session, contrast-enhanced computed tomography scans revealed the formation of multiple gas-containing liver abscesses. **(D, E)** Subsequently, the patient underwent percutaneous drainage (PCD). **(F)** One month after PCD, contrast-enhanced computed tomography scans showed an increase in tumor size and multiple new metastases in the liver (arrow).

TABLE 1 Baseline characteristics of patients with liver abscesses.

Patient	Age/sex	DM	Diagnosis	Surgical history	Portal vein thrombosis	Child–Pugh class
1	64/M	–	HCC	Pulmonary lobectomy	–	A
2	69/M	–	Liver metastasis of CCA	Whipple surgery	–	A
3	69/M	–	HCC	Partial hepatectomy RFA Biliary incision for stone removal	–	B
4.1	47/M	–	Liver metastasis of SPN	Whipple surgery	+	A
4.2	49/M	–	Liver metastasis of SPN	Whipple surgery	+	B
5	74/M	+	HCC	RFA	+	A
6	79/F	–	HCC	Meningioma resection	+	A
7	65/M	–	HCC	Partial hepatectomy RFA	–	A
8	62/M	–	Liver metastasis of CCA	Whipple surgery	–	A
9	56/F	–	HCC	Partial hepatectomy	–	A
10	65/M	–	Liver metastasis of VPC	PTCD	–	A
11	61/F	–	Liver metastasis of GIST	GIST and meningioma resection	–	A
12	54/M	–	Liver metastasis of CCA	Whipple surgery	–	A
13	64/F	+	HCC	PTCD	–	B
14	78/M	+	HCC	–	–	A
15	64/M	+	HCC	PTCD	–	A

Patients 4.1 and 4.2 refer to the same patient who presented twice with liver abscesses. The total number of patients was 15, and the total number of TACE cases was 16.
CCA, cholangiocarcinoma; DM, diabetes mellitus; F, female; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; M, male; PTCD, percutaneous transhepatic cholangial drainage; RFA, radiofrequency ablation; SPN, solid pseudopapillary neoplasm; TACE, transarterial chemoembolization.

TABLE 2 Clinical characteristics and surgical management of patients with liver abscesses.

Patient	TACE sessions	Treated tumor diameter (cm)	Embolic materials	TACE duration (min)	Symptoms	Diagnosis time (day)	Management	Blood or pus culture
1	1	12.3	IOE+GSP	60	Fever, chills, abdominal pain	30	AT	–
2	1	5.3	DEB	150	Fever, chills, abdominal pain	17	AT+PCD	*E. faecalis*
3	2	5.6	IOE	105	Abdominal pain	40	AT+PCD	*E. coli*
4.1	2	12.4	IOE	90	Fever	23	AT+PCD	Negative
4.2	9	5.9	IOE	120	Fever	6	AT+PCD	Negative
5	6	8.0	IOE	90	Fever	15	AT+PCD	Negative
6	2	4.9	DEB	180	Fever, chills	10	AT+PCD	*E. coli*; *E. faecalis*
7	1	2.8	IOE	90	Fever, chills	3	AT+PCD	*K. pneumonia*
8	2	5.0	DEB	120	Fever	13	AT+PCD	*E. faecalis*
9	1	7.4	DEB	180	Fever, chills	11	AT+PCD	*E. coli*

(Continued)

TABLE 2 Continued

Patient	TACE sessions	Treated tumor diameter (cm)	Embolic materials	TACE duration (min)	Symptoms	Diagnosis time (day)	Management	Blood or pus culture
10	2	9.4	DEB	90	Fever, abdominal pain	15	AT+PCD	*E. faecalis*
11	1	9.7	DEB	90	Fever	10	AT+PCD	Negative
12	1	3.5	DEB	60	Fever	12	AT+PCD	*E. coli*; *M. morgan*
13	1	5.0	DEB	150	Fever, chills	4	AT+PCD	Negative
14	1	8.6	DEB	90	Fever	3	AT+PCD	Negative
15	4	7.6	DEB	80	Fever, chills, abdominal pain	15	AT+PCD	*E. faecalis*

AT, therapy; Diagnosis time, time from TACE to the discovery of liver abscess; DEB, drug-eluting beads; E. coli, Escherichia coli; E. faecalis, Enterococcus faecalis; GSP, gelatin sponge particles; IOE, iodized-oil emulsion; K. pneumonia, Klebsiella pneumonia; M. morgan, Morganella morgan; PCD, percutaneous drainage; TACE, transarterial chemoembolization.

bile duct (8, 20). Meanwhile, the local toxicity of chemoembolic agents and the embolization of bile duct feeding vessels resulting from TACE may lead to bile duct injury (21). In this study, patients had received an average of 2.31 ± 2.24 TACE sessions at the time of liver abscess formation; among them, one patient developed liver abscesses after the second and ninth TACE sessions. Bile duct injury following TACE may enable opportunistic pathogens to colonize the bile duct and enter the liver parenchyma, where they undergo rapid proliferation within the local ischemic and hypoxic microenvironment after TACE, thus leading to liver abscess formation (6, 22, 23).

Diabetes is also thought to be a predisposing factor for liver abscess formation after TACE.

Diabetes is also thought to be a predisposing factor for liver abscess formation after TACE (9, 10). On the one hand, the chronic inflammatory state that arises in diabetes leads to continuous

TABLE 3 Treatment and follow-up findings in patients with liver abscesses.

Patient	Treatment	Infection controlled	Follow-up time (months)	Abscess healed	Tumor response	Drainage tube removed	Drainage tube removal time (days)	Survival status
1	AB	+	18	+	SD	NA	NA	Survival
2	AB+PCD	+	5	+	SD	+	73	Death
3	AB+PCD	+	4	–	PD	–	NA	Survival
4.1	AB+PCD	+	49	+	PR	+	75	Survival
4.2	AB+PCD	+	23	+	PD	+	420	Survival
5	AB+PCD	+	7	–	PR	–	NA	Death
6	AB+PCD	+	10	+	PD	+	120	Death
7	AB+PCD	+	3	–	SD	–	NA	Death
8	AB+PCD	+	6	–	PD	–	NA	Death
9	AB+PCD	+	4	–	PR	–	NA	Death
10	AB+PCD	+	5	–	SD	–	NA	Death
11	AB+PCD	+	18	–	SD	–	NA	Death
12	AB+PCD	+	9	+	PD	+	90	Death
13	AB+PCD	+	2	–	SD	–	NA	Death
14	AB+PCD	+	6	+	PD	+	117	Death
15	AB+PCD	+	9	–	PD	–	NA	Death

Tumor response was the response observed after the confirmation of liver abscess by contrast-enhanced computed tomography/magnetic resonance imaging scanning within 1–3 months after the formation of liver abscess. The mRECIST criteria were used as the evaluation standard. AB, antibiotic; CR, complete response; NA, not applicable; PCD, percutaneous drainage; PD, progressive disease; PR, partial response; SD, stable disease; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

reactive oxygen species (ROS) production, and ROS stimulate the expression of pro-inflammatory cytokines by activating transcription factors such as nuclear factor-kappa B (24). In addition, in diabetic patients, excess adipose tissue secretes pro-inflammatory cytokines, further amplifying oxidative stress (25). On the other hand, hyperglycemia in diabetes is thought to cause dysfunction of the immune response, which fails to control the spread of invading pathogens in diabetic subjects, through the following mechanisms: impairment of cytokine production, leukocyte recruitment inhibition, defects in pathogen recognition, neutrophil dysfunction, macrophage dysfunction, natural killer cell dysfunction, and inhibition of antibodies and complement effector (26).

In this study, 87.5% of the tumors had a maximum diameter of >5 cm. Large tumor size and extensive use of embolic materials may have simultaneously increased the extent of intrahepatic necrosis and the risk of abscess formation (9). In addition, portal vein tumor thrombosis and gelatin sponge use have been associated with liver abscess formation (8). Owing to the small sample size, we could not examine the association between these risk factors and liver abscess formation.

It has been suggested that patients with liver metastases are more likely to develop liver abscesses after TACE compared with hepatocellular carcinoma (HCC) (27). In HCC, high concentrations of chemoembolic agents in the tumor tissue after infusion can be achieved because the arteries that feed the tumor and intratumoral blood space are mostly dilated. On the contrary, the feeding artery and the intratumoral blood space of metastatic liver tumors are not usually dilated, thus decreasing the intratumoral concentration of chemoembolic agents. This may result in higher concentrations of the chemoembolic agents in the surrounding liver parenchyma and initiation of biliary epithelial damage. Additionally, HCC is mostly noted in cirrhotic livers that are known to have dilation of the perivascular plexus, which can serve as a porto-arterial shunt and compensate for the decreased arterial flow (27, 28). Therefore, they may be the reasons for the higher incidence of liver abscesses in patients with liver metastases.

Prevention of the occurrence of liver abscesses after TACE has been the focus of clinical attention. Incidentally, it is unreasonable and unnecessary to use antibiotics prophylactically for all patients with TACE. It has been shown that prophylactic antibiotics reduce the incidence of liver abscess formation in patients with bile duct injury (29, 30). Moreover, previous studies have shown that the incidence of liver abscess formation does not increase among patients without bile duct injury who do not receive prophylactic antibiotics (30, 31). Therefore, stratification according to risk factors is more reasonable for the administration of prophylactic antibiotics before TACE.

In this study, 15 of 1,387 (1.1%) patients undergoing TACE subsequently developed liver abscesses; this rate was similar to that previously reported (5–13, 16, 19, 27, 32–36) (Table 4). Although the incidence of liver abscess formation after TACE is low, it is necessary to grasp its clinical symptoms. In our study, the most common symptom reported by patients was fever (93.8%), followed by chills (43.8%) and abdominal pain (31.3%). However, PES characterized by fever, right upper quadrant pain, nausea, and vomiting is the most common adverse event, affecting approximately 60%–80% of patients. PES generally occurs immediately after TACE, with fever peaking within 2 days after TACE, and it is often self-limiting and does not require antibiotic treatment (37–40). In contrast, in this study, the mean interval from

TABLE 4 Review of literature on the incidence of liver abscess after TACE.

Study	Year	Place	Study design	Setting	No. of patients who underwent TACE	No. of patients with liver abscesses after TACE	Incidence of liver abscess after TACE
Zhu et al.	2022	China, mainland	Retrospective	2 hospitals	11,524	84	0.72%
Arslan et al.	2019	Turkey	Retrospective	1 hospital	163	4	2.45%
Jia et al.	2018	China, mainland	Retrospective	4 hospitals	3,129	23	0.74%
Sun et al.	2017	China, mainland	Retrospective	1 hospital	1,480	5	0.34%
Lv et al.	2016	China, mainland	Retrospective	1 hospital	3,613	21	0.58%
Shin et al.	2014	South, Korea	Retrospective	1 hospital	5,299	72	1.36%
Xia et al.	2006	China, mainland	Retrospective	1 hospital	1,348	3	0.22%
Huang et al.	2003	China, Taiwan	Retrospective	1 hospital	1,347	7	0.52%
Kim et al.	2001	United States	Retrospective	1 hospital	157	7	4.46%
Song et al.	2001	South, Korea	Retrospective	1 hospital	2,439	14	0.57%
Tarazov et al.	2000	Russia	Retrospective	1 hospital	282	6	2.13%
Gates et al.	1999	United States	Retrospective	1 hospital	251	1	0.40%
Sakamoto et al.	1998	Japan	Retrospective	1 hospital	850	5	0.59%

(Continued)

TABLE 4 Continued

Study	Year	Place	Study design	Setting	No. of patients who underwent TACE	No. of patients with liver abscesses after TACE	Incidence of liver abscess after TACE
Chen et al.	1997	China, Taiwan	Retrospective	1 hospital	289	5	1.73%
de Baère et al.	1996	France	Retrospective	1 hospital	181	3	1.66%
Farinati et al.	1996	Italy	Retrospective	1 hospital	72	2	2.78%
Reed et al.	1994	United States	Retrospective	1 hospital	227	6	2.64%

TACE, transarterial chemoembolization.

TACE to the discovery of liver abscess was 14.19 ± 9.21 (range, 3–40) days, suggesting that the onset of liver abscess formation occurred later than PES at the time point after TACE. Furthermore, chills are frequently observed among patients with liver abscesses but not in those with PES, which may help differentiate between these outcomes.

This study has some limitations. First, as this was a single-center study, the results cannot be generalized. Second, as this was a retrospective study, our data integrity may not be as high as that in prospective studies or clinical trials. Third, as some patients after TACE were subsequently lost to follow-up, this study may have underestimated the incidence of liver abscess formation following TACE. Fourth, the low incidence of post-TACE liver abscess and small sample size precluded comparative analyses of prognosis in patients without liver abscess formation. Moreover, we could not use univariate and multivariate Cox regression statistical methods to reach more robust conclusions.

In conclusion, patients with liver abscess formation following TACE for malignant liver tumors had a long drainage tube removal time after PCD and even required continuous canalization. Although liver abscess formation was not directly related to death, it indirectly led to poor prognosis in these patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

This study protocol was reviewed and approved by the Ethics Committee of Shengjing Hospital of China Medical University (protocol number 2022PS1175K). The studies were conducted in accordance with the local legislation and institutional requirements. Owing to the retrospective nature of this study, the informed consent requirement was waived.

Author contributions

YW: Writing – original draft. ZC: Data curation, Funding acquisition, Writing – review & editing. JHZ: Formal Analysis, Writing – review & editing. ZL: Data curation, Writing – original draft. JZ: Writing – review & editing.

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Conflict of interest

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

Publisher's note

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