Retrospective Cohort Study

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TACE-HAIC combined with targeted therapy and immunotherapy versus TACE alone for hepatocellular carcinoma with portal vein tumour thrombus: a propensity score matching study

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Background: The long-term survival of patients with hepatocellular carcinoma (HCC) with portal vein tumour thrombus (PVTT) is poor. Systemic therapy, transcatheter arterial chemoembolization (TACE), and hepatic artery infusion chemotherapy are widely used in HCC patients with PVTT. This study aims to explore the efficacy of combining systemic therapy with transarterial-based therapy in HCC patients with PVTT.

Materials and methods: The authors retrospectively reviewed data of HCC patients with PVTT treated with combination therapy (TACE-hepatic artery infusion chemotherapy with tyrosine kinase inhibitors and PD-1 inhibitors) or TACE alone in SYSUCC from 2011 to 2020. The overall survival (OS), progression-free survival, and overall response rate were compared. Propensity score matching was used to minimize confounding bias.

Results: A total of 743 HCC patients with PVTT received combination therapy ($n = 139$) or TACE alone ($n = 604$). After propensity score matching, the overall response rate was significantly higher in the combination group than in the TACE group [42.1% vs. 5.0%, $P < 0.001$ (response evaluation criteria in solid tumours); 53.7% vs. 7.8%, $P < 0.001$ (modified response evaluation criteria in solid tumours)]. The combination group showed significantly better OS than the TACE group (median OS not reached vs. 10.4 months, $P < 0.001$). The median progression-free survival of the combination and TACE groups was 14.8 and 2.3 months ($P < 0.001$), respectively. Tumour downstaging followed by salvage liver resection was significantly more common for the combination therapy group than for TACE group (46.3% vs. 4.5%, $P < 0.001$). After salvage liver resection, 31.6% (30/95) and 1.7% (3/179) of the patients achieved a pathological complete response in the combination and TACE groups, respectively ($P < 0.001$). The grade 3/4 adverse events rates were similar between the two groups (28.1% vs. 35.9%, $P = 0.092$).

Conclusion: Compared with TACE alone, combination therapy was safe enough and resulted in survival benefits. This is a promising treatment option for HCC patients with PVTT.

Keywords: combination therapy, hepatocellular carcinoma, portal vein tumour thrombus, propensity score matching

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HIGHLIGHTS

- The benefit of combined systemic therapy with transarterial therapy for hepatocellular carcinoma patients with portal vein tumour thrombus was unknown.
- Combination therapy resulted in better survival outcomes than transcatheter arterial chemoembolization alone.
- Combination therapy had better conversion and pathologic complete response rates.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and third leading cause of cancer-related deaths worldwide[1]. HCC is characterized by vascular invasion, particularly of the portal vein, resulting in portal vein tumour thrombus (PVTT) in 10–40% of patients at the time of HCC diagnosis. The extent of this malignancy has direct adverse effects on liver function and portal hypertension[2]. The prognosis of these patients is extremely poor, with a median overall survival (OS) of approximately three months without treatment[3].

The Barcelona Clinic Liver Cancer staging system recommends systemic therapy with targeted therapy and immunotherapy for HCC patients with PVTT[4,5]. Several studies have found that transcatheter arterial chemoembolization (TACE) provides survival benefits for HCC patients with PVTT[6]. TACE is also recommended by the NCCN guidelines and CNLC guidelines[7,8]. Furthermore, TACE is one of the most commonly used treatments for HCC patients with PVTT in China, as economic conditions can restrict the use of systemic therapy for some patients[9].

FOLFOX-based hepatic artery infusion chemotherapy (HAIC) is an effective treatment for advanced HCC and has been reported to significantly improve OS compared to TACE alone[10]. Our previous study showed that combining HAIC with TACE further improved the overall response rate (ORR) and survival in patients with unresectable HCC[11]; however, no potent combination regimen has been reported in HCC patients with PVTT. In this study, the efficacy and safety of combination therapy [TACE-HAIC combined with tyrosine kinase inhibitors (TKIs) and PD-1 inhibitors] were compared with those of TACE alone in the treatment of HCC patients with PVTT.

Methods

Study design

We retrospectively reviewed data of HCC patients with PVTT in Sun Yat-Sen University Cancer Center (SYSUCC) from 2011 to 2020. This study was approved by the Institutional Review Board of SYSUCC and was performed in accordance with Declaration of Helsinki of 1975, as revised in 1983. The Ethics Committee of SYSUCC approved this study (approval number: B2022-312-01). This study is fully compliant with the STROCSS criteria, and the completed checklist has been provided[12], Supplemental Digital Content 1, http://links.lww.com/JS9/A236. In addition, this study has been registered with the unique identifying number: Researchregistry8488, https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6371d3849c5d740021cc519e/.

HCC was diagnosed by radiological examination based on the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases criteria[13,14]. The extent of PVTT was classified according to the classification of PVTT proposed in 1987 by the Liver Cancer Study Group of Japan and cited by Lu J and colleagues as[2]: Vp1, tumour thrombus distal but not in second-order branches of the main portal vein; Vp2, tumour thrombus in second-order branches; Vp3, tumour thrombus in first-order branches; and Vp4, tumour thrombus in the main trunk, contralateral to the trunk, or both.

The inclusion criteria were as follows: patients with HCC and (a) PVTT (Vp1–4) treated by TACE or combination therapy (TACE-HAIC combined with TKIs or PD-1 inhibitors) as initial treatment; (b) aged 18–75 years; (c) Child-Pugh A or B liver function; (d) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (e) adequate haematologic blood counts (white blood cell count $>3\times10^9$/L, absolute neutrophil count $>1.5\times10^9$/L, platelet count $>10\times10^9$/L, haemoglobin concentration > 85 g/L). The exclusion criteria were as follows: (a) severe underlying cardiac, pulmonary, or renal disease; (b) history of a second primary malignant tumour; (c) incomplete medical data; and (d) loss to follow-up.

Treatment protocol

TACE was performed as described in our previous study[15]. Briefly, chemoembolization was performed using 30 mg/m^2 of epirubicin, 200 mg/m^2 of carboplatin, and 4 mg/m^2 of mitomycin C, mixed with 2–5 mL lipiodol. Up to 20 mL of additional pure lipiodol were injected into the tumour-feeding artery until stasis of blood flow was observed in the target artery. Repeated TACE was performed at intervals of 3–4 weeks.

The TACE-HAIC regimen named by us as the SYSUCC procedure has been described in detail in our previous study[11]. Briefly, chemoembolization was performed using 30 mg/m^2 of epirubicin mixed with 2–5 mL of lipiodol, followed by pure lipiodol. Then, a catheter was placed and fixed in the tumour-feeding artery for the FOLFOX-based chemotherapy infusion at the following dosages: 85 mg/m^2 of oxaliplatin infusion for 2 h; 400 mg/m^2 of leucovorin infusion for 2 h; 400 mg/m^2 of 5-FU bolus, and 2400 mg/m^2 of continuous 5-FU infusion for 46 h or 1200 mg/m^2 of continuous 5-FU infusion for 23 h. Repeated TACE-HAIC was performed at intervals of 3–4 weeks.

The TKIs used in this study included lenvatinib (12 mg/d for bodyweight $\geq$ 60 kg or 8 mg/d for bodyweight < 60 kg orally once daily), sorafenib (400 mg twice a day) or apatinib (250–500 mg orally once daily). Administration of lenvatinib, apatinib, or sorafenib began on the first day post-TACE-HAIC and continued until disease progression or serious treatment-related toxicity occurred. PD-1 inhibitors were intravenously administered on the first day post-TACE-HAIC as follows: 200 mg of camrelizumab, 200 mg of sintilimab, 240 mg of toripalimab, or 200 mg of tislelizumab, every three to four weeks (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). The choice of TKIs and PD-1 inhibitors was based on the price of the drugs, the corresponding charity gift policy, the patient's local health insurance reimbursement status, and the patient's preference.

The opportunity for tumour downstaging followed by salvage liver resection was determined by a multidisciplinary team of surgeons, radiologists, and anesthesiologists. Surgery was performed by one of three experienced surgeons (Y.Y., B.L., Y.Z.) with 15 years of experience in hepatic resection. The procedure for hepatic resection has been described in our previous study[11]. Thrombectomy was performed based on the location and extent of PVTT[16]. En bloc resection was performed in patients with PVTT located within the resected area. The PVTT was extracted from the opened stump of the portal vein if it protruded into the main portal vein beyond the resection plane.

Assessment of response

The tumour responses were evaluated 3–4 weeks after treatment using intravenous contrast-enhanced computed tomography or MRI. The radiological responses of the tumours were evaluated by two experienced radiologists based on the modified response evaluation criteria in solid tumours (mRECIST) and modified response evaluation criteria in solid tumours (RECIST) 1.1 criteria[17,18]. The tumour responses were classified into the following groups: complete response, partial response (PR), stable disease, and progressive disease. ORR was the sum of the complete response and PR rates. The disease control rate (DCR) was defined as the ORR plus stable disease rate.

Follow-up

Liver computed tomography /MRI scans and blood tests, including serum alpha-fetoprotein, liver function, complete blood count, and coagulation parameters, were performed before each course. After resection, patients were followed-up 1 month later, once every 3–4 months in the first 2 years, and then once every 4–6 months thereafter. This study was censored on 1 September 2021. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria version 5.0.

Statistical analysis

Propensity score matching (PSM) analysis was used to reduce selection bias and balance the patient characteristics (Detailed in Supplementary Material, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). Continuous variables were compared using independent-sample or paired-sample *t*-tests. Categorical variables were compared using the χ^2 test. The Mann–Whitney U test and χ^2 test were used to compare the clinical parameters between the two groups. Progression-free survival (PFS) was defined as the time from the first treatment to clinical progression or death. OS was defined as the time from the first treatment to death. OS and PFS were analyzed using Kaplan–Meier curves and compared using the log-rank test. Univariate and multivariate analyses were performed to identify parameters for predicting survival using the Cox proportional hazards model. All analyses were two-sided, and *P* values less than 0.05 were considered statistically significant. All statistical analyses and PSM analyses were performed using R version 3.5.0 and SPSS 24.0.

Results

Patient characteristics

Of the 743 patients included in this study, 604 received TACE and 139 received combination therapy with median follow-up periods of 79.9 and 23.6 months, respectively. The flowchart of this study is illustrated in Figure 1. Age, platelets count, albumin, and total bilirubin levels were significantly different between the two groups. PSM generated 95 and 179 patients in the combination therapy and TACE groups, respectively. Baseline patient characteristics, including tumour type (nodular/infiltrative), main tumour size, tumour number, tumour involvement (hemiliver/hemilivers), and extent of PVTT were well matched between the groups after PSM (all $P > 0.2$) (Table 1).

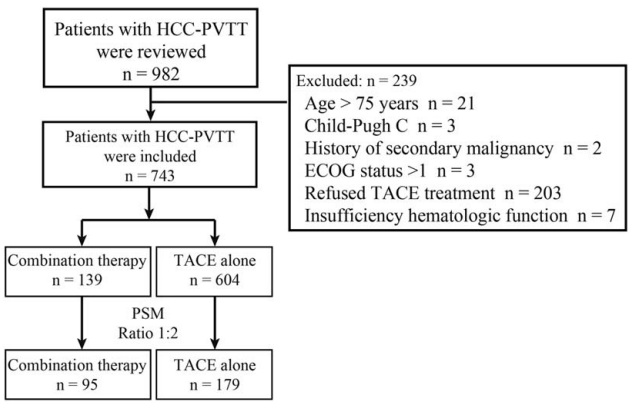

Figure 1. Flow diagram of HCC patients with PVTT who underwent combination therapy or TACE. ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; PSM, propensity score matching; PVTT, portal vein tumour thrombus; TACE, transcatheter arterial chemoembolization.

Before PSM, patients in the combination therapy group were treated with a total of 285 cycles of TACE-HAIC (range: 1–6, median: 2), and patients in the TACE group were treated with a total of 1265 cycles of TACE (range: 1–5, median: 2).

Tumour responses

The tumour responses of the patients before PSM are shown in Table 2. Based on the RECIST criteria, patients in the combination therapy group achieved higher rates of PR (39.6% vs. 5.1%, $P < 0.001$), DCR (78.4% vs. 60.6%, $P = 0.005$), and ORR (39.6% vs. 5.1%, $P < 0.001$) than those in the TACE group. Patients in the combination therapy group also achieved higher PR (50.4% vs. 5.79%, $P < 0.001$), DCR (78.4% vs. 62.1%, $P = 0.02$), and ORR (51.8% vs. 6.6%, $P = 0.016$) than those in the TACE group according to the mRECIST criteria.

After PSM, patients in the combination therapy group achieved higher PR (42.1% vs. 5.0%, $P < 0.001$), DCR (78.9% vs. 59.2%, $P = 0.010$), and ORR (42.1% vs. 5.0%, $P < 0.001$) than those in the TACE group based on the RECIST criteria. Similarly, according to the mRECIST criteria, patients in the combination therapy group achieved higher PR (51.6% vs. 6.7%, $P < 0.001$), DCR (81.1% vs. 62.0%, $P < 0.001$), and ORR (53.7% vs. 7.8%, $P < 0.001$) than those in the TACE group (Table 3). In addition, PVTT responses achieved a higher ratio of PR in the combination therapy group than in the TACE group according to RECIST (49.6% vs. 8.7%, $P < 0.01$) (Fig. 2).

After PSM, tumour downstaging followed by salvage liver resection was performed in 44 patients (44/95, 46.3%) in the combination therapy group, and 30 (30/95, 31.6%) of these patients achieved pathological complete response (pCR) (Supplementary Figure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). Eight patients (8/179, 4.5%) in the TACE group underwent salvage liver resection, and three (3/179, 1.7%) achieved pCR (31.6% vs. 1.7%, $P < 0.001$). No significant difference in OS ($P = 0.46$) or PFS ($P = 0.94$) was observed between the two groups (Supplementary Figure 2, Supplemental Digital Content 2, http://links.lww.com/JS9/A237).

Survival outcomes

Considering the long-term death rates for the entire group of patients before PSM, 55 (55/139, 39.6%) patients in the combination therapy group and 570 (570/604, 94.4%) patients in the TACE group had died by the time of the study (Fig. 3A, B). The results of the univariate and multivariate analyses of PFS and OS are shown in Supplementary Tables 2–5, Supplemental Digital Content 2, http://links.lww.com/JS9/A237. Multivariate Cox regression analysis showed that combination therapy was an independent risk factor for OS (hazard ratio = 0.216; 95% CI = 0.157–0.299, $P < 0.001$; Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/A237) and PFS (hazard ratio = 0.200; 95% CI = 0.152–0.264, $P < 0.001$; Supplementary Table 5, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). The corresponding long-term death rates after PSM was 38.9% (37/95) in the combination therapy group and 95.5% (171/179) in the TACE group (Fig. 3C, D). The

Table 1

Baseline characteristics of HCC patients with portal vein tumour thrombus.

	Before matching			After matching		
Variables	**Combination therapy ($n=139$)**	**TACE ($n=604$)**	***P***	**Combination therapy ($n=95$)**	**TACE ($n=179$)**	***P***
Sex			0.507			0.550
Male	130 (93.5)	562 (93.0)		88 (92.6)	165 (92.2)	
Female	9 (6.5)	42 (7.0)		7 (7.4)	14 (7.8)	
Age (years)			< 0.001			0.400
≥ 60	36 (25.9)	260 (43.0)		27 (28.4)	55 (30.7)	
< 60	103 (74.1)	344 (57.0)		68 (71.6)	124 (69.3)	
PLT (10^9/l)			0.001			0.321
≥ 100	133 (95.7)	523 (86.6)		90 (94.7)	173 (96.6)	
< 100	6 (4.3)	81 (13.4)		5 (5.3)	6 (3.4)	
ALT(U/l)			0.094			0.798
> 40	70 (50.4)	344 (57.0)		40 (42.1)	79 (44.1)	
≤ 40	69 (49.6)	260 (43.0)		55 (57.9)	100 (55.9)	
AST(U/l)			0.074			0.203
> 40	59 (42.4)	300 (49.7)		30 (31.6)	67 (37.4)	
≤ 40	80 (57.6)	304 (50.3)		65 (68.4)	112 (62.6)	
ALB(g/l)			0.002			0.416
≥ 35	125 (89.9)	481 (79.6)		86 (90.5)	159 (88.8)	
< 35	14 (10.1)	123 (20.4)		9 (9.5)	20 (11.2)	
TBIL(μmol/l)			< 0.001			0.171
> 17.1	50 (36.0)	7 (1.2)		7 (7.4)	7 (3.9)	
≤ 17.1	89 (64.0)	597 (98.8)		88 (92.6)	172 (96.1)	
PT (s)			0.260			0.416
> 13.5	21 (15.1)	108 (17.9)		9 (9.5)	20 (11.2)	
≤ 13.5	118 (84.9)	496 (82.1)		86 (90.5)	159 (88.8)	
AFP (ng/ml)			0.445			0.349
≤ 400	83 (59.7)	354 (58.6)		42 (44.2)	85 (47.5)	
> 400	56 (40.3)	250 (41.4)		53 (55.8)	94 (52.5)	
HBsAg			0.362			0.538
Positive	118 (84.9)	522 (86.4)		80 (84.2)	150 (83.8)	
Negative	21 (15.1)	82 (13.6)		15 (15.8)	29 (16.2)	
Main tumour size (cm)			0.405			0.438
≥ 10 cm	71 (51.1)	299 (49.5)		45 (47.4)	88 (49.2)	
< 10 cm	68 (48.9)	305 (50.5)		50 (52.6)	91 (50.8)	
Tumour type			0.210			0.514
Nodular	25 (18.0)	130 (21.5)		19 (20.0)	37 (20.7)	
Infiltrative	114 (82.0)	474 (78.5)		76 (80.0)	142 (79.3)	
PVTT			0.223			0.496
vp1–2	31 (22.3)	115 (19.0)		22 (23.2)	40 (22.3)	
vp3–4	108 (77.7)	489 (81.0)		73 (76.8)	139 (77.7)	
HVTT			0.147			0.370
Absent	98 (70.5)	395 (65.4)		67 (70.5)	131 (73.2)	
Present	41 (29.5)	209 (34.6)		28 (29.5)	48 (26.8)	
Imaging cirrhosis			0.266			0.382
Absent	61 (43.9)	245 (40.6)		42 (44.2)	84 (46.9)	
Present	78 (56.1)	359 (59.4)		53 (55.8)	95 (53.1)	
Tumour involvement			0.261			0.513
Hemiliver	72 (51.8)	312 (51.7)		44 (46.3)	84 (46.9)	
Both hemilivers	67 (48.2)	292 (48.3)		51 (53.7)	95 (53.1)	
Distant Metastasis			0.062			0.278
Absent	131 (94.2)	537 (88.9)		89 (93.7)	159 (88.8)	
Present	8 (5.7)	67 (11.1)		6 (6.3)	20 (11.2)	
Lung	5 (3.6)	55 (9.1)		4 (4.2)	17 (9.7)	
Bone	2 (1.4)	5 (0.8)		1 (1.05)	2 (1.0)	
Lung and bone	1 (0.7)	5 (0.8)		1 (1.05)	1 (0.5)	
Spleen	—	1 (0.2)		—	—	
Peritoneum	—	1 (0.2)		—	—	
Conversion to resection			< 0.001			< 0.001
Yes	55 (39.6)	11 (1.8)		44 (46.3)	8 (4.5)	
No	84 (60.4)	593 (98.2)		51 (53.7)	171 (95.5)	

Values are presented as *n* (%).

P values were calculated using a two-sided χ^2 test.

AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; HVTT, hepatic vein tumour thrombus; PLT, platelet; PT, prothrombin time; PVTT, portal vein tumour thrombus; TACE, transcatheter arterial chemoembolization; TBIL, total bilirubin.

1-year, 2-year, and 3-year OS rates were 75.7%, 57.8%, and 53.4% in the combination therapy group and 35.3%, 15.4%, and 9.7% in the TACE group, respectively. The median OS was 10.4 months in the TACE group, but not reached in the combination therapy group. The median PFS was 14.8 and 2.3 months in the combination therapy and TACE groups, respectively. The 1-year and 2-year PFS rates were 61.2% and 24.5% in the combination therapy group and 10.6% and 3.9% in the TACE group, respectively.

We further studied the prognosis of the different treatment subgroups comparing to TACE treatment (subgroups: 1. TACE-HAIC plus TKIs; 2. TACE-HAIC plus immunotherapy; 3. TACE-HAIC plus TKIs and immunotherapy). Before PSM, the respective 1-year and 2-year OS rates were 64.3% and 46.9% in the TACE-HAIC

Table 2

Treatment efficacy evaluated by RECIST and mRECIST criteria before PSM.

	RECIST criteria			mRECIST criteria		
	Combination therapy ($n=139$)	TACE ($n=604$)	*P*	Combination therapy ($n=139$)	TACE ($n=604$)	*P*
Complete response	0	0	—	2 (1.4)	5 (0.8)	—
Partial response	55 (39.6)	31 (5.1)	<0.001	70 (50.4)	35 (5.79)	<0.001
Stable disease	54 (38.8)	335 (55.5)	<0.001	37 (26.6)	335 (55.5)	<0.001
Progressive disease	30 (21.6)	238 (39.4)	0.005	30 (21.6)	229 (37.9)	0.002
Overall response	55 (39.6)	31 (5.1)	<0.001	72 (51.8)	40 (6.6)	0.016
Disease control	109 (78.4)	366 (60.6)	0.005	109 (78.4)	375 (62.1)	0.002

Summary of best response.
Values are presented as *n* (%).
P values were calculated using a two-sided χ^2 test.
mRECIST, modified response evaluation criteria in solid tumours; PSM, propensity score matching; RECIST, response evaluation criteria in solid tumours; TACE, transcatheter arterial chemoembolization.

plus TKIs subgroup, 63.6% and 50.9% in the TACE-HAIC plus immunotherapy subgroup, and 79.2% and 64.0% in the TACE-HAIC plus TKIs and immunotherapy subgroup ($P < 0.001$) (Supplementary Figure 3A, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). The respective 1-year and 2-year PFS rates were 55.6% and 34.1% in the TACE-HAIC plus TKIs subgroup, 81.8% and 65.5% in the TACE-HAIC plus immunotherapy subgroup, and 58.7% and 11.8% in the TACE-HAIC plus TKIs and immunotherapy subgroup ($P < 0.001$) (Supplementary Figure 3B, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). After PSM, the respective 1-year and 2-year OS rates were 71.9% and 53.1% in the TACE-HAIC plus TKIs subgroup, 71.4% and 47.6% in the TACE-HAIC plus immunotherapy subgroup, and 77.7% and 62.4% in the TACE-HAIC and TKI plus immunotherapy subgroup ($P = 0.001$) (Supplementary Figure 3C, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). The respective 1-year and 2-year PFS rates were 58.4% and 32.5%, 85.7%, and 57.1%, and 58.9% and 12.1% in the TACE-HAIC plus TKIs, TACE-HAIC plus immunotherapy, and TACE-HAIC plus TKIs and immunotherapy subgroups ($P < 0.001$) (Supplementary Figure 3D, Supplemental Digital Content 2, http://links.lww.com/JS9/A237).

Whether the effectiveness of treatment is independent on the extent of Vp is a question well worth analysis. We compared OS and PFS in Vp1–2 and Vp3–4 patients who received combination therapy and found no statistical difference in prognosis between the two groups (Supplementary Figure 4A-B, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). In addition, we compared the OS and PFS in patients with Vp1–2 and Vp3–4 who received TACE. Unlike in the combination treatment group, the prognosis of the Vp1–2 patients were better than that of the Vp3–4 patients in the TACE group (Supplementary Figure 4C-D, Supplemental Digital Content 2, http://links.lww.com/JS9/A237).

To study whether combination therapy could provide better survival outcomes in HCC patients with more severe PVTT, OS and PFS were compared among Vp3–4 patients in each group (Supplementary Figure 5, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). After PSM, the 1-year, 2-year, and 3-year OS rates were 75.4%, 55.0%, and 52.9% in the combination therapy group and 24.4%, 6.6%, and 4.4% in the TACE group, respectively ($P < 0.001$) (Supplemental Figure 5C, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). Additionally, the 1-year and 2-year PFS rates were 56.7% and 23.9%, respectively, in the combination therapy group were 5.0% and 0.7%, respectively, in the TACE group ($P < 0.001$) (Supplemental Figure 5D, Supplemental Digital Content 2, http://links.lww.com/JS9/A237). The median OS was not reached and 7.3 months, and the median PFS was 11.4 and 2.3 months in the combination therapy and TACE groups, respectively. These results showed that combination therapy resulted in significantly better survival outcomes in patients with more severe PVTT.

Treatment safety

The adverse events in the two groups are listed in Table 4. Leukopenia (39.6% vs. 24.3%), hand–foot skin reaction

Table 3

Treatment efficacy evaluated by RECIST and mRECIST criteria after PSM.

	RECIST criteria			mRECIST criteria		
	Combination therapy ($n=95$)	TACE ($n=179$)	*P*	Combination therapy ($n=95$)	TACE ($n=179$)	*P*
Complete response	0	0	—	2 (2.1)	2 (1.1)	—
Partial response	40 (42.1)	9 (5.0)	<0.001	49 (51.6)	12 (6.7)	<0.001
Stable disease	35 (36.8)	97 (54.2)	<0.001	26 (27.4)	97 (54.2)	<0.001
Progressive disease	20 (21.1)	73 (40.8)	0.003	18 (18.9)	68 (38.0)	0.001
Overall response	40 (42.1)	9 (5.0)	<0.001	51 (53.7)	14 (7.8)	<0.001
Disease control	75 (78.9)	106 (59.2)	0.010	77 (81.1)	111 (62.0)	<0.001

Summary of best response.
Values are presented as *n* (%).
P values were calculated using a two-sided χ^2 test.
mRECIST, modified response evaluation criteria in solid tumours; PSM, propensity score matching; RECIST, response evaluation criteria in solid tumours; TACE, transcatheter arterial chemoembolization.

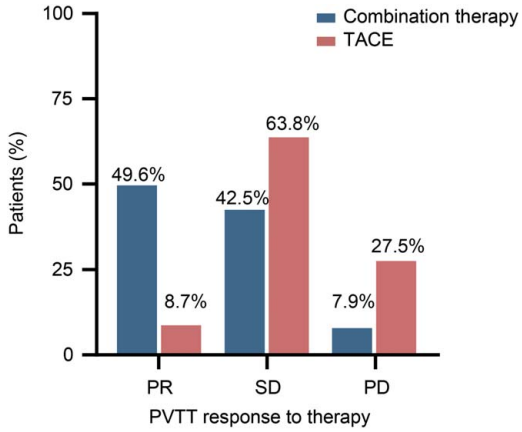

Figure 2. Histogram depicting response of PVTT using the RECIST criteria in the combination therapy and TACE groups after PSM. PSM, propensity score matching; PVTT, portal vein tumour thrombus; RECIST, response evaluation criteria in solid tumours TACE, transcatheter arterial chemoembolization.

(28.1% vs. 0.8%), vomiting (55.4% vs. 41.6%), diarrhoea (23.0% vs. 9.6%), elevated aminotransferase levels (79.9% vs. 64.4%), hyperbilirubinemia (60.4% vs. 49.2%), and hypoalbuminemia (68.3% vs. 47.6%) were insignificantly higher in the combination therapy group than in the TACE group. However, the frequency of grade 3–4 abdominal pain (20.1% vs. 33.3%) was significantly higher in the TACE group than that in the combination therapy group. Finally, the overall incidence of serious adverse events was higher in the TACE group than the combination therapy group (35.9% vs. 28.1%, $P = 0.092$).

Discussion

This retrospective study showed that combination therapy using TACE-HAIC with TKIs or PD-1 inhibitors conferred significantly better long-term OS and PFS than TACE alone in the treatment of HCC with PVTT. The combination therapy group also exhibited a higher ORR with better tumour remission, and nearly half of the patients in this group were able to undergo salvage liver resection after tumour downstaging, with 31.6% of the patients achieving pCR. These results indicate that combination therapy is superior to TACE in the treatment of HCC patients with PVTT.

Several previous studies have explored the efficacy and safety of local treatment (TACE alone or HAIC alone) or combination therapy in advanced HCC[19,20]. However, our study has the following advantages. First, the population of advanced HCC included in previous studies was highly heterogeneous, including patients with distant metastases, portal vein carcinoma thrombosis or hepatic vein carcinoma thrombosis, and multiple intrahepatic lesions. Our study focuses on HCC patients with PVTT. Second, local treatment modalities in previous studies were mainly HAIC or TACE alone, whereas our study mainly explored the local treatment modality of TACE combined with HAIC. Our previous studies have found that TACE-HAIC demonstrated a higher conversion rate and PFS benefit than c-TACE in patients with initially unresectable HCC[11]. The current study further confirms the efficacy of TACE-HAIC in combination with targeted therapy and immunotherapy in HCC patients with PVTT. Third, we strengthened the reliability of the results by minimizing the bias between the two groups using PSM. We found that combination treatment significantly increased the tumour downstaging and salvage live resection rate and the pathologic complete response rate. These data also outperformed the results reported in other studies (HAIC combined with targeted therapy or HAIC combined with immunotherapy alone).

PVTT is an important prognostic factor in patients with HCC. Although a variety of treatments has been proposed, no treatment has been universally accepted[10]. However, sorafenib has been shown to effectively prolong long-term survival in patients with advanced HCC[21]. Many studies have shown that it is uncommon for PVTT to completely block portal venous blood flow because PVTT is formed slowly, and abundant collateral circulation occurs so that the liver still receives its blood supply from the portal vein and hepatic artery. TACE treatment is based on the fact that both HCC and PVTT receive their blood supply mainly through the hepatic artery. A previous study that compared the efficacy of TACE and sorafenib in patients with advanced-stage HCC showed promising outcomes[22]. Other studies have identified TACE as a treatment option for HCC patients with PVTT who have adequate hepatic functional reserve and good performance status[23]. Finally, TACE is commonly used for HCC patients with PVTT in Eastern countries[2].

Despite advances in TACE treatment, HCC patients with PVTT still have a poor prognosis[2]. Emerging medical evidence has demonstrated that FOLFOX-HAIC results in a favourable tumour response in HCC patients with PVTT[10]. HAIC, a transarterial therapy, can deliver high doses of chemotherapy directly through the hepatic artery to the tumour to improve ORR, while reducing systemic drug concentrations to minimize toxicity. Our previous study demonstrated that combining TACE with HAIC resulted in a survival benefit for selected patients with advanced HCC[11]. Moreover, previous studies have shown a synergistic effect of antiangiogenic agents with immunotherapy, resulting in promising antitumor activity in treating advanced HCC[24,25]. Thus, combination therapy using transarterial treatment with immune checkpoint inhibitors and antiangiogenic agents can be used as a new treatment strategy for patients with advanced HCC[26].

The effect of the combination therapy used in this study can be attributed to several factors. First, chemotherapeutic agents can induce not only tumour apoptosis through DNA damage and cytoplasmic effects, but also immunogenic cell death of tumour cells. This effect can elicit antitumor immune responses to further promote the efficacy of immunotherapy[27]. Second, TKIs are multikinase inhibitors with antiproliferative and antiangiogenic activities that can counteract hypoxia-induced angiogenesis by TACE-HAIC[28]. Furthermore, TKIs therapy has been shown to produce synergistic benefits when combined with anti-PD-1 therapy by regulating the tumour immune microenvironment and promoting tumour T-cell infiltration[29]. Third, anti-PD-1 therapy can facilitate immune attacks on tumours to enhance the immune response against tumour cells[30].

One interesting finding was that there was no statistical difference in prognosis between the Vp1–2 and Vp3–4 patients who received combination therapy (TACE-HAIC plus TKI and immunotherapy). Contrary to our previous clinical observations, that is, that PVTT severity is associated with poor prognosis, we found the prognosis of HCC patients receiving combination therapy was not associated with the extent of PVTT. This suggests that combination therapy can be effective in patients

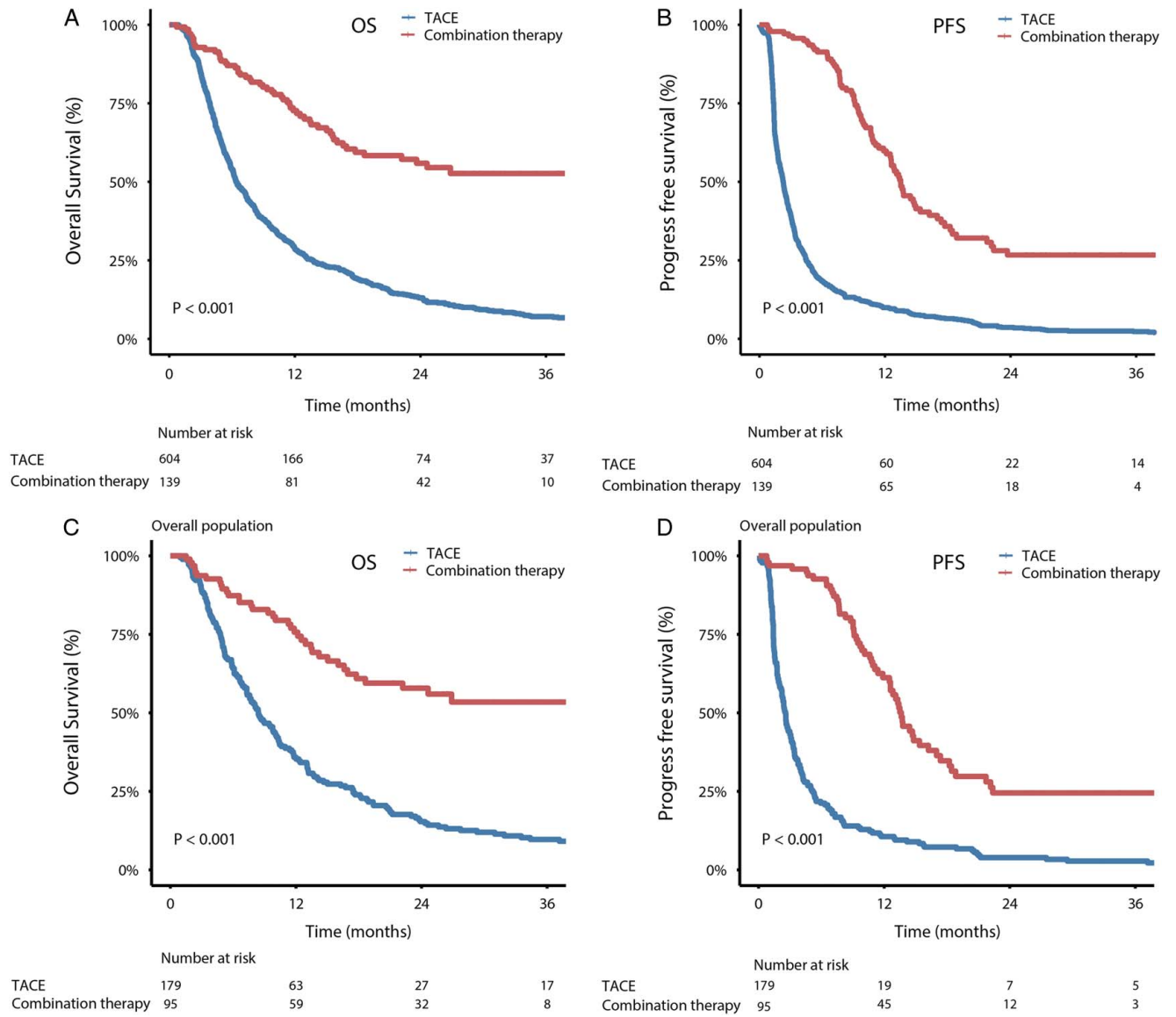

Figure 3. Kaplan–Meier survival curves comparing OS and PFS among patients who underwent combination therapy versus TACE before (A–B) and after PSM (C, D). The combination therapy group had significantly longer OS and better PFS than the TACE group (all $P < 0.001$). OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization.

regardless of the extent of PVTT. A possible explanation could be that the prognostic impact of PVTT severity was offset by the significant efficacy of the combination regimen. However, this result needs to be further studied and confounding factors need to be excluded.

Recent studies have reported that various combination therapies can significantly improve the rate of salvage liver resection after tumour downstaging, resulting in pCR. A resection rate of 46.8% and a pCR rate of 25.8% were observed in unresectable HCC patients treated by TACE combined with lenvatinib plus PD-1 inhibitors[25]. Another study reported that the resection rate was 15.9% and the pCR rate was 9.5% in patients with initially unresectable HCC treated with TKIs and PD-1 inhibitors[26]. In this study, the salvage liver resection rate after tumour downstaging was 46.3%, and the pCR rate was 31.6% in the combination therapy group of HCC patients with PVTT.

This study had some limitations. First, as we found that the efficacy of combination therapy was significantly better than that of TACE alone, TACE therapy is now increasingly uncommon in our clinical practice, inevitably resulting in the inability to enrol patients in the TACE group during the same period. Second, this was a retrospective study, resulting in inherent selection bias, and PSM analysis could not completely eliminate all these biases. Third, the mean follow-up period was not long enough in the combination therapy group, and a longer follow-up time is required in future studies to verify the effect of combination therapy. Fourth, this was a single-centre study, which may have limited the generalizability of the results. However, the good results of combining TACE-HAIC with TKIs and PD-1 inhibitors provided clues for further subsequent studies to follow.

In conclusion, compared with TACE alone, combination therapy using TACE-HAIC with TKIs and PD-1 inhibitors

Table 4

Treatment-related adverse events.

	Any grade (cases)			Grade 3–4 (cases)		
Adverse event	**Combination therapy ($n=139$)**	**TACE ($n=604$)**	***P***	**Combination therapy ($n=139$)**	**TACE ($n=604$)**	***P***
Leukopenia	55 (39.6)	147 (24.3)	<0.001	14 (10.1)	38 (6.3)	0.138
Thrombocytopenia	54 (38.8)	240 (39.7)	0.923	12 (8.63)	58 (9.6)	0.872
Hand–foot skin reaction	39 (28.1)	5 (0.8)	<0.001	6 (4.3)	0	—
Rash	22 (15.8)	0	—	2 (1.4)	0	—
Vomiting	77 (55.4)	251 (41.6)	0.003	32 (24.0)	135 (22.4)	0.910
Diarrhoea	32 (23.0)	58 (9.6)	<0.001	1 (0.7)	3 (0.4)	0.564
Abdominal pain	57 (41.0)	301 (49.8)	0.060	28 (20.1)	201 (33.3)	0.002
Elevated ALT	111 (79.9)	389 (64.4)	<0.001	22 (15.8)	87 (14.4)	0.690
Hyperbilirubinemia	84 (60.4)	297 (49.2)	0.019	3 (2.2)	7 (1.2)	0.407
Hypoalbuminemia	95 (68.3)	288 (47.6)	<0.001	11 (7.9)	32 (5.2)	0.230

Values are presented as *n* (%).
P values were calculated using a two-sided χ^2 test.
TACE, transcatheter arterial chemoembolization.

resulted in favourable treatment responses and improved long-term survival outcomes. Moreover, a significant proportion of patients could receive curative treatment using salvage liver resection after tumour downstaging for HCC with PVTT. Therefore, combination therapy may be an ideal treatment strategy for HCC patients with PVTT.

Ethical approval

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and the Ethics Committee of Sun Yat-Sen University Cancer Center approved this study (approval number [B2022-312-01]).

Consent to participate

Written informed consent was obtained before treatment.

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Author contribution

Study concept and design: Y.Y., B.L. Drafting of the manuscript: Y.Y., W.H., Z.Y. Acquisition of data, analysis and interpretation of data: Y.Y., W.H., J.Q., Y.Z., Z.H., Y.S., Z.L. Critical revision of the manuscript: Y.Y., W.Y.L., B.L., M.C. Statistical analysis: Y.Y., W.H., Z.Y. Study supervision: Y.Y., BL. All authors read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

1. Name of the registry: Research registry
2. Unique Identifying number or registration ID: Research-registry8488
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-theregistry#home/registrationdetails/6371d3849c5d740021cc519e/

Data statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Guarantor

Prof. Yunfei Yuan acts as guarantor for the report and accepts responsibility for the work.

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