Efficacy of transarterial chemoembolization-hepatic arterial infusion chemotherapy combined with targeted therapy and immunotherapy in hepatocellular carcinoma with portal vein tumor thrombosis

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Abstract. Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) presents a notable therapeutic challenge. The efficacy of transarterial chemoembolization (TACE) combined with hepatic arterial infusion chemotherapy (HAIC) and systemic therapy using tyrosine kinase inhibitor and programmed cell death protein 1 inhibitor has not been fully explored. In the present study, the clinical data from 251 patients with HCC and PVTT treated at Harbin Medical University Cancer Hospital (Harbin, China) between January 2021 and December 2022 were retrospectively analyzed. Patients were divided into four groups: TACE-HAIC + lenvatinib + camrelizumab (Group 1; n=16), TACE + lenvatinib + camrelizumab (Group 2; n=90), HAIC + lenvatinib + camrelizumab (Group 3; n=102) and TACE alone (Group 4; n=43). Clinical data included demographics, preoperative indices, tumor characteristics, medical history, performance status, liver function, pre-treatment α-fetoprotein levels and adverse events. Survival outcomes [overall survival (OS) and progression-free survival (PFS)] were analyzed using Kaplan-Meier survival curves. Group 1 exhibited significantly longer OS and PFS times compared with Group 4 (both $P<0.05$). Adverse events, including fatigue, diarrhea, nausea, vomiting and immune-related pneumonitis, were more frequent in Group 1 (all $P<0.001$). Group 2 also showed improved OS and PFS times compared with Group 4 (both $P<0.05$), with notable differences in adverse event profiles. Group 3 demonstrated superior survival outcomes compared with Group 4 ($P<0.05$), although with a higher incidence of adverse events. No significant differences in OS or PFS times were observed between Groups 1 and 3, or between Groups 2 and 3, indicating comparable efficacy between TACE-HAIC + lenvatinib + camrelizumab and HAIC + lenvatinib + camrelizumab. In conclusion, TACE-HAIC combined with lenvatinib and camrelizumab significantly improved both OS and PFS times in patients with HCC and PVTT compared with TACE alone, despite a higher incidence of adverse events. This combination therapy represents a promising treatment strategy for this patient population, offering enhanced survival benefits.

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Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; CR, complete remission; PR, partial remission; SD, stable disease

Key words: hepatocellular carcinoma, portal vein tumor thrombosis, transarterial chemoembolization, hepatic arterial infusion chemotherapy, overall survival, progression-free survival

Introduction

Hepatocellular carcinoma (HCC) ranks as the fifth most prevalent carcinoma globally and holds the position of the third most frequent cause of tumor-associated mortality (1). At present, approximately one-half of all HCC cases are reported in China, which is largely attributed to the widespread incidence of chronic hepatitis within the nation (2,3). Regarding cancer-related mortality in China, HCC ranks as the second leading cause of cancer-related death among males and the third leading cause in females (4). A notable aspect of HCC is its tendency for vascular infiltration, especially in the portal vein. This often results in portal vein tumor thrombosis (PVTT), affecting 10-40% of individuals at the time of HCC diagnosis. Such malignant progression detrimentally impacts hepatic functionality and causes portal hypertension (5). The life expectancy for patients afflicted by this condition is significantly shortened, with a median overall survival (OS) time of ~3 months in the absence of therapeutic intervention (6).

Currently, the use of systemic treatments involving targeted therapy and immunotherapies for HCC with PVTT has been relatively accepted and advocated for (7,8). Research indicates that transarterial chemoembolization (TACE) enhances survival prospects for HCC sufferers with PVTT (9). The National Comprehensive Cancer Network (NCCN) and Chinese National Liver Cancer (CNLC) guidelines also endorse TACE (10,11). Moreover, in China, TACE is frequently utilized to treat HCC with PVTT, particularly due to economic factors that restrict access to systemic therapies for some patients (12).

In the realm of liver cancer treatment, hepatic arterial infusion chemotherapy (HAIC), building upon the foundation of the folinic acid, fluorouracil and oxaliplatin (FOLFOX) regimen, has demonstrated efficacy in managing advanced HCC. Studies have revealed that HAIC, in comparison to TACE as a sole therapy, markedly enhances patient OS time (13,14). It is evident that the integration of HAIC with TACE not only amplifies the overall response rate (ORR) but also the survival rates in individuals grappling with inoperable HCC (15). Nevertheless, for patients with HCC who are afflicted with PVTT, a potent combination therapy remains unexplored. The present study compares the effectiveness and safety of a combined regimen, TACE/HAIC with tyrosine kinase inhibitors (TKIs) and programmed cell death protein 1 (PD-1) inhibitors, against TACE in isolation, specifically targeting patients with HCC plus PVTT.

Materials and methods

Study cohort. The clinical data from 251 patients diagnosed with HCC combined with portal vein tumor thrombosis (PVTT) who were admitted to Harbin Medical University Cancer Hospital (Harbin, China) between January 2021 and December 2022 were retrospectively collected and analyzed. Hepatic cancer diagnoses were confirmed using imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), adhering to guidelines set by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases (16,17). PVTT severity was subclassified based on established PVTT criteria (18) as follows: Vp1, characterized by a tumor thrombus presence distal to the main portal vein, excluding the secondary branches; Vp2, indicating a tumor thrombus within secondary branches; Vp3, characterized by a tumor thrombus in the primary branches; and Vp4, denoting a tumor thrombus in the main trunk, its opposite counterpart or both.

The following inclusion criteria were applied: i) Individuals diagnosed with primary HCC combined with PVTT (Vp1-4 stages) who received initial treatment either through TACE or a combination therapy that included TACE-HAIC along with a TKI or a PD-1 inhibitor; ii) participants within the age range of 18 to 75 years; iii) patients whose liver function was categorized as Child-Pugh class A or B; iv) patients with an Eastern Cooperative Oncology Group (ECOG) performance status score ≤1.

The following exclusion criteria were applied: i) Individuals diagnosed with severe diseases of the heart, lungs or kidneys; ii) patients with a prior diagnosis of another distinct primary cancer; iii) patients with medical records that were not comprehensive; and iv) patients who were not available for subsequent follow-up.

Finally, 251 patients were included and divided into four groups based on the treatment method, with 16 administered TACE + HAIC + lenvatinib + camrelizumab (Group 1), 90 administered TACE + lenvatinib + camrelizumab (Group 2), 102 administered HAIC + lenvatinib + camrelizumab (Group 3) and 43 administered TACE alone (Group 4). The present study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital (approval no. YD2024-11). All patients provided written informed consent for participation in the study, and all procedures were carried out in accordance with the Declaration of Helsinki.

Medication protocol. The process of TACE was executed as previously described (19). This procedure entailed utilizing a combination of 20-30 mg pirarubicin and 50 mg oxaliplatin/loplatin, amalgamated with 2-10 ml of an iodized oil-based agent. The injection of up to 20 ml of this agent directly into the arteries feeding the tumor was performed to achieve stasis in blood flow within the target artery. Repeated sessions of TACE were scheduled every 3-4 weeks.

The TACE-HAIC protocol was performed as previously described (15). The chemoembolization process involved combining 30 mg/m^2 doxorubicin with 2-10 ml of an iodized oil-based agent, followed by the administration of the pure agent. A catheter was then inserted and fixed in the artery supplying the tumor. This was used for administering FOLFOX-based chemotherapy, comprising 85 mg/m^2 oxaliplatin over 2 h, 400 mg/m^2 calcium folinate over the same duration, a 400-mg/m^2 fluorouracil (5-FU) bolus, and a choice between a 2,400-mg/m^2 continuous 5-FU infusion over 46 h or a 1,200-mg/m^2 continuous infusion over 23 h. These TACE-HAIC sessions were repeated every 3-4 weeks.

The TKI applied in the present study was lenvatinib (daily; 12 mg orally for a body weight ≥60 kg and 8 mg for a body weight <60 kg). Lenvatinib administration began on the first day after TACE-HAIC and continued until disease progression or the onset of severe treatment-associated toxicity. On the first day after TACE-HAIC, a PD-1 inhibitor was administered intravenously every 3-4 weeks, consisting of either 200 mg carrelizumab or 200 mg sindilizumab.

Treatment response evaluation. Between 3 and 4 weeks after treatment, tumor responses were assessed using enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Two skilled radiologists examined the radiological behavior of the tumor, referencing the modified Response Evaluation Criteria in Solid Tumors (20). The tumor responses were subclassified into four categories: Complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease. The ORR was used to represent the combined CR and PR rates. Additionally, the disease control rate (DCR) was defined as the sum of the ORR and the SD rate, reflecting the proportion of patients with CR, PR, or SD.

Follow-up. Prior to each treatment cycle, patients underwent liver imaging through CT or MRI, accompanied by various blood examinations. These included tests for serum α-fetoprotein, liver function, whole blood profile and coagulation assessments. Post-surgical follow-ups were scheduled at 1-month intervals initially, and subsequently once every 3-4 months during the first 2 years. The assessment of any adverse events was conducted in accordance with the Common Toxicity Criteria version 5.0 set by the National Cancer Institute (21).

Imaging protocols. To ensure consistency in imaging characteristics, resolution and sensitivity to tumor features, all patients underwent contrast-enhanced CT or MRI scans with standardized protocols. CT was performed with a 64-slice multi-detector scanner (slice thickness, 1 mm) using a standard contrast agent (iohexol), while MRI utilized a 1.5T or 3T scanner with gadolinium-based contrast agents. Tumors were characterized by size, location and enhancement patterns, with HCC diagnosed based on hypervascularity and washout patterns. PVTT was evaluated for thrombus involvement and extension. Imaging data were reviewed by two independent radiologists to ensure consistency. Disagreements between the radiologists regarding tumor response assessment were resolved by following a predefined decision hierarchy: i) Discussion between the two radiologists to reach a consensus, ii) if no agreement was reached, a third radiologist, blinded to the initial assessments, was consulted to provide the final decision. Quality control measures were implemented across all sites, including regular calibration and training. These standardized protocols aimed to minimize variation in tumor assessment and ensure reliable imaging results.

Statistical analysis. All statistical analyses were performed using SPSS version 22.0 (IBM Corp.) and R software version 4.3.0 (https://www.r-project.org/). Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed continuous variables are presented as the mean ± standard deviation and were compared using one-way analysis of variance, followed by Tukey's post hoc test for multiple pairwise comparisons. Non-normally distributed continuous variables are presented as the median (interquartile range) and were compared using the Kruskal-Wallis test, followed by Dunn's test with Bonferroni's correction for post hoc multiple comparisons. Categorical variables are expressed as frequencies and percentages. Intergroup comparisons were initially performed using the χ^2 test. In cases where the expected count in >20% of the cells was <5, Fisher's exact test was used instead. To adjust for multiple comparisons among categorical variables, Bonferroni's correction was applied where appropriate. All statistical tests were two-sided, and P<0.05 was considered to indicate a statistically significant difference. Adjusted P-values following multiple comparisons are reported where applicable.

Results

Baseline characteristics. The baseline characteristics and statistical comparisons of the patients in the four treatment groups are summarized in Table I. Significant differences were observed in several demographic and clinical variables. The mean age differed significantly among the groups (P=0.024), although no statistically significant difference was found in the post hoc analysis. Sex distribution also varied (P=0.018), with group 4 exhibiting a notably higher proportion of female patients (34.9%) compared with the other groups. There were no significant differences in preoperative liver function parameters, including aspartate aminotransferase, alanine aminotransferase, total bilirubin and prothrombin time, among the groups (all P>0.05). However, serum albumin levels differed significantly (P=0.010), with post hoc analysis indicating that group 2 had significantly higher albumin levels compared with group 3 (P=0.009). Tumor burden differed markedly between groups. For example, tumor count (P<0.001) showed significant variation, with group 3 predominantly comprising patients with ≤3 tumors (94.1%), whereas group 2 had a majority with >3 tumors (94.4%). Similarly, maximum tumor diameter significantly varied across groups (P<0.001), with group 2 including exclusively patients with tumors ≥100 mm, while the majority of patients in group 4 (76.7%) and group 3 (60.8%) had tumors <100 mm. Post hoc comparisons revealed significant differences between group 1 and group 2 (P<0.05 for both tumor count and size). Regarding medical history, significant differences were found in the prevalence of hepatitis B and hepatitis C infection (both P<0.001). Hepatitis B was more common in groups 2, 3 and 4, while hepatitis C was predominantly seen in group 1 (93.8%). The prevalence of liver cirrhosis and ascites also differed significantly among the groups (both P<0.001), with group 1 having the lowest incidence of cirrhosis (25.0%) and the highest incidence of ascites (81.3%). ECOG performance status and pretreatment α-fetoprotein levels did not differ significantly among the groups (P=0.285 and P=0.299, respectively). However, Child-Pugh classification differed significantly (P<0.001), with post hoc analysis showing a higher proportion of Class B patients in group 3 compared with group 2 (P<0.001). Treatment-related adverse events (AEs) were markedly more frequent and severe in group 1 compared with other groups. All patients in Group 1 (100.0%) experienced fatigue, diarrhea, nausea and vomiting, decreased appetite, weight loss, joint pain, and there was a high incidence of other immune-related AEs such as rash (68.8%), oral mucositis (93.8%), hand-foot syndrome (75.0%), bleeding events (93.8%), and immune-related pneumonitis (93.8%). These AEs were significantly more frequent than those observed in group 2 (all P<0.001), as confirmed by post hoc analysis with Bonferroni's correction.

Comparison between the patients with HCC treated with TACE + HAIC + lenvatinib + camrelizumab (group 1) and those treated with TACE (group 4). The Kaplan-Meier survival curves for OS and progression-free survival (PFS) in patients with HCC and PVTT treated with TACE-HAIC combined with lenvatinib and camrelizumab (group 1) vs. TACE alone (group 4) are shown in Fig. 1. For OS, patients in group 1 exhibited a significantly longer survival time compared with those in group 4 (P=0.03). Regarding PFS time, group 1 also showed marked improvement over group 4 (P=0.01). The survival analysis underscores the enhanced benefit of adding lenvatinib and camrelizumab to TACE-HAIC in terms of extending the progression-free interval. These results collectively suggest

Table I. Clinical information of patients with hepatocellular carcinoma in the four treatment groups.

Characteristic	Group 1	Group 2	Group 3	Group 4	P-value	Between-group variations
Age, years	53.38±7.24	54.07±10.02	57.49±8.59	53.58±9.35	0.024	NS
Sex, n (%)					0.018	NS
Male	15 (93.75)	77 (85.6)	87 (85.3)	28 (65.12)		
Female	1 (6.25)	13 (14.4)	15 (14.7)	15 (34.88)		
Preoperative indices						
AST, U/l	54.00 (42.25, 102.50)	52.00 (35.50, 91.50)	53.00 (38.00, 82.25)	54.00 (39.00, 83.00)	0.926	NS
ALT, U/l	40.50 (25.00, 53.25)	35.00 (26.00, 63.00)	36.50 (24.00, 57.75)	37.00 (26.00, 52.00)	0.955	NS
TB, μmol/l	20.30 (13.40, 26.25)	20.40 (13.90, 26.60)	20.35 (13.68, 28.38)	20.10 (16.90, 28.10)	0.961	NS
PT, sec	12.20 (11.65, 12.88)	12.00 (11.35, 12.95)	12.30 (11.78, 13.00)	12.50 (11.90, 13.10)	0.167	NS
Albumin, g/l	40.90 (36.93, 42.10)	39.45 (35.80, 43.30)	37.65 (34.28, 40.80)	39.50 (36.00, 42.30)	0.01	Group 2 vs. group 3, P=0.009
Tumor count, n (%)					<0.001	Group 1 vs. group 2, P=0.0047
≤3	6 (37.5)	5 (5.6)	96 (94.1)	27 (62.8)		
>3	10 (62.5)	85 (94.4)	6 (5.9)	16 (37.2)		
Maximum tumor diameter, n (%)					<0.001	Group 1 vs. group 2, P<0.001
<100 mm	8 (50.0)	0 (0.0)	62 (60.8)	33 (76.7)		
≥100 mm	8 (50.0)	90 (100.0)	40 (39.2)	10 (23.3)		
Medical history, n (%)						
Hepatitis B	4 (25.0)	70 (77.8)	73 (71.6)	34 (79.1)	<0.001	Group 1 vs. group 2, P<0.001
Hepatitis C	15 (93.8)	4 (4.4)	15 (14.7)	3 (7.00)	<0.001	Group 1 vs. group 2. P<0.001
Cirrhosis	4 (25.0)	67 (74.4)	75 (73.5)	33 (76.7)	<0.001	Group 1 vs. group 2, P<0.001
Ascites	13 (81.3)	18 (20.0)	34 (33.3)	2 (4.7)	<0.001	Group 1 vs. group 2, P<0.001
ECOG, n (%)					0.285	NS
<1	12 (75.0)	51 (56.7)	51 (50.0)	32 (74.4)		
≥1	4 (25.0)	39 (43.3)	51 (50.0)	11 (25.6)		
Child-Pugh classification					<0.001	Group 2 vs. group 3, P<0.001
A	14 (87.5)	90 (100.0)	80 (78.4)	39 (90.7)		
B	2 (12.5)	0 (0.0)	22 (21.6)	4 (9.3)		
Pre-treatment AFP, n (%)					0.299	NS
<400 ng/ml	7 (43.8)	46 (51.1)	54 (52.9)	16 (38.1)		
≥400 ng/ml	9 (56.2)	44 (48.9)	48 (47.1)	27 (61.9)		
Treatment-associated adverse events, n (%)						
Fatigue	16 (100.0)	6 (6.7)	46 (45.1)	5 (11.6)	<0.001	Group 1 vs. group 2, P<0.001
Abdominal pain	15 (93.8)	0 (0.0)	42 (41.2)	2 (4.7)	<0.001	Group 1 vs. group 2, P<0.001
Diarrhea	16 (100.0)	7 (7.8)	39 (38.2)	2 (4.7)	<0.001	Group 1 vs. group 2, P<0.001
Nausea and vomiting	16 (100.0)	5 (5.6)	37 (36.3)	5 (11.6)	<0.001	Group 1 vs. group 2, P<0.001
Decreased appetite	16 (100.0)	7 (7.8)	42 (41.2)	8 (18.6)	<0.001	Group 1 vs. group 2, P<0.001
Weight loss	16 (100.0)	7 (7.8)	49 (48.0)	8 (18.6)	<0.001	Group 1 vs. group 2, P<0.001
Rash	11 (68.8)	8 (8.9)	26 (25.5)	0 (0.0)	<0.001	Group 1 vs. group 2, P<0.001
Oral mucositis	15 (93.8)	6 (6.7)	12 (11.8)	0 (0.0)	<0.001	Group 1 vs. group 2, P<0.001
Hand-foot syndrome	12 (75.0)	2 (2.2)	14 (13.7)	0 (0.0)	<0.001	Group 1 vs. group 2, P<0.001
Joint pain	16 (100.0)	2 (2.2)	9 (8.8)	0 (0.0)	<0.001	Group 1 vs. group 2, P<0.001

Table I. Continued.

Characteristic	Group 1	Group 2	Group 3	Group 4	P-value	Between-group variations
Bleeding events	15 (93.8)	4 (4.4)	30 (29.4)	0 (0.0)	<0.001	Group 1 vs. group 2, P<0.001
Immune-related pneumonitis	15 (93.8)	2 (2.2)	9 (8.8)	0 (0.0)	<0.001	Group 1 vs. group 2, P<0.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin; PT, prothrombin time; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; NS, no significance.

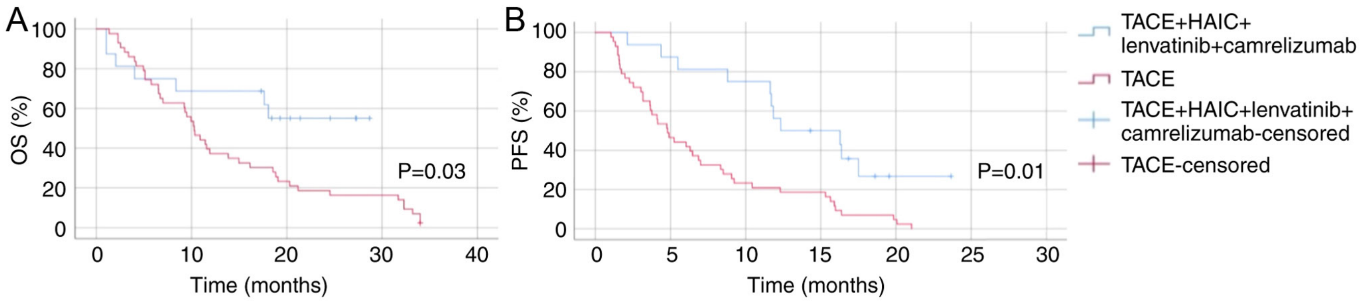

Figure 1. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between the patients with hepatocellular carcinoma treated with TACE + HAIC + lenvatinib + camrelizumab (group 1) and those treated with TACE (group 4). OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

that TACE-HAIC combined with lenvatinib and camrelizumab significantly improves both OS and PFS times in patients with HCC and PVTT, compared with TACE alone, highlighting the potential of this combination therapy as a more effective treatment strategy.

Comparison between the patients with HCC treated with TACE + lenvatinib + camrelizumab (group 2) and those treated with TACE (group 4). Group 2 demonstrated a significantly longer OS time compared with group 4 (P=0.002; Fig. 2). The median OS time for group 2, which was ~18 months, extended beyond the observed period, while the median OS time for group 4 was ~10 months. The 12-month survival rate was notably higher in group 2, underscoring the improved efficacy of the combined treatment. In terms of PFS time, group 2 also showed a substantial improvement over group 4 (P<0.001; Fig. 2). The median PFS for group 2 was markedly longer, with a higher proportion of patients remaining progression-free at 12 months compared with group 4, which had a median PFS time of ~5 months. These findings indicate that TACE combined with lenvatinib and camrelizumab significantly enhances both OS and PFS time in patients with HCC and PVTT, compared with TACE alone.

Comparison between the patients with HCC treated with HAIC + lenvatinib + camrelizumab (group 3) and those treated with TACE (group 4). Group 3 exhibited a significantly prolonged OS time compared with group 4 (P<0.001; Fig. 3). Regarding PFS, group 3 also showed a marked improvement over group 4 (P<0.001; Fig. 3). The median PFS time for group 3 was markedly longer, with a higher proportion of patients remaining progression-free at 12 months compared with group 4, which had a median PFS time of ~5 months. These results demonstrate that HAIC combined with lenvatinib and camrelizumab significantly enhances both OS and PFS times in patients with HCC and PVTT compared with TACE alone, supporting the efficacy of this combination therapy.

Comparison between the patients with HCC treated with TACE + HAIC + lenvatinib + camrelizumab (group 1) and those treated with HAIC + lenvatinib + camrelizumab (group 3). For OS time, there was no significant difference between group 1 and group 3 (P>0.05; Fig. 4). Both groups exhibited similar survival rates over the observed period, indicating that the addition of TACE to HAIC combined with lenvatinib and camrelizumab did not significantly impact OS. In terms of PFS, group 1 demonstrated a slight improvement over group 3, but there was no significant difference (P>0.05; Fig. 4). Overall, these results indicate that while there is a slight non-significant improvement in PFS with the addition of TACE to HAIC combined with lenvatinib and camrelizumab, the overall survival benefit remains similar between the two treatment strategies.

Comparison between the patients with HCC treated with TACE + lenvatinib + camrelizumab (group 2), those treated with both TACE + HAIC + lenvatinib + camrelizumab (group 1) and those treated with HAIC + lenvatinib + camrelizumab (group 3). In terms of OS time, there was no significant difference between group 2 (TACE + lenvatinib + camrelizumab) and group 3 (HAIC + lenvatinib + camrelizumab) (P>0.05; Fig. 5). Both groups demonstrated comparable survival profiles throughout the observation period, suggesting that substituting TACE with HAIC in combination with lenvatinib

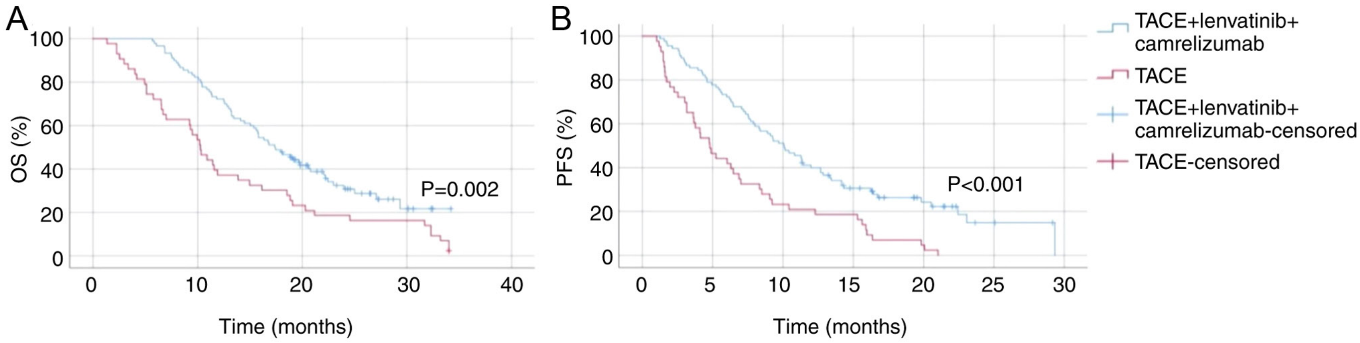

Figure 2. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between the patients with hepatocellular carcinoma treated with TACE + lenvatinib + camrelizumab (group 2) and those treated with TACE (group 4). OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization.

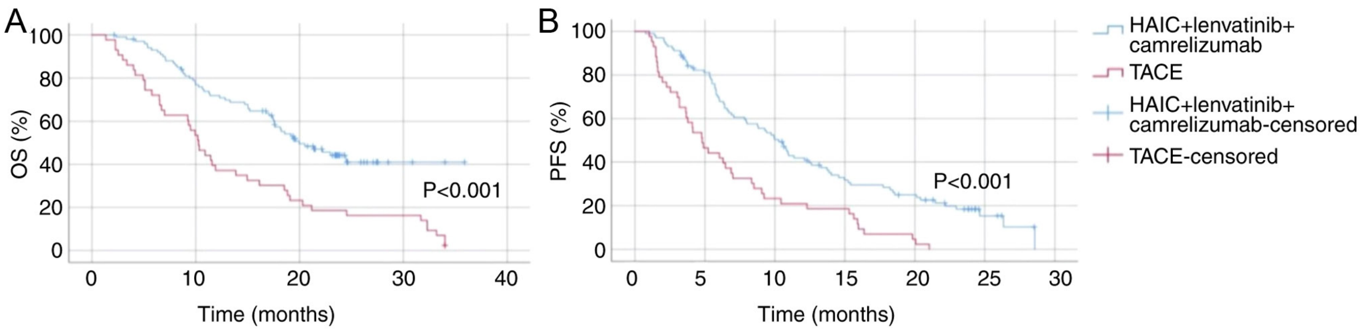

Figure 3. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between the patients with hepatocellular carcinoma treated with HAIC + lenvatinib + camrelizumab (group 3) and those treated with TACE (group 4). OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

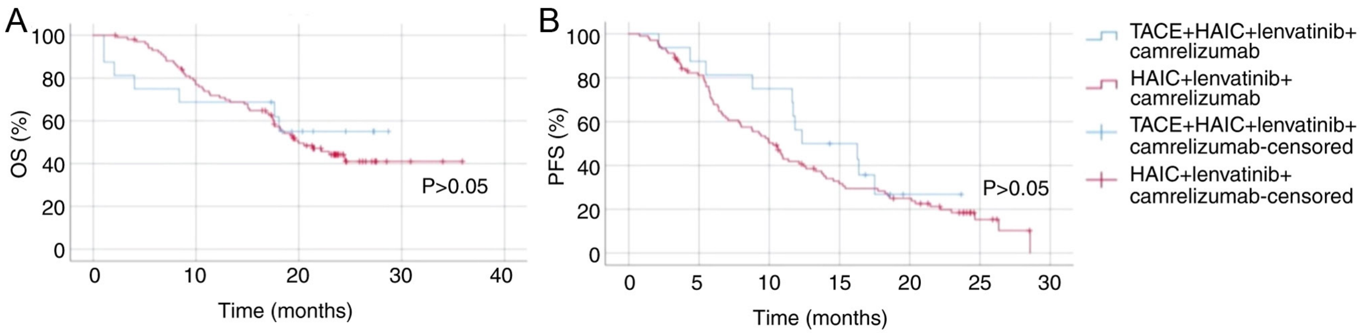

Figure 4. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between the patients with hepatocellular carcinoma treated with TACE + HAIC + lenvatinib + camrelizumab (group 1) and those treated with HAIC + lenvatinib + camrelizumab (group 3). OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

and camrelizumab did not result in a marked improvement in OS time. Regarding PFS time, no statistically significant difference was observed between group 2 and group 3 either (P>0.05; Fig. 5), further indicating similar clinical efficacy between the two approaches. Similarly, when comparing group 1 (TACE + HAIC + lenvatinib + camrelizumab) with group 2, no significant difference in OS time was identified (P>0.05; Fig. 6). Both regimens yielded parallel survival trends, implying that the addition of HAIC to the TACE-based regimen did not significantly enhance OS time. Although a slight numerical improvement in PFS time was noted in group 1 compared with group 2, it did not reach statistical significance (P>0.05; Fig. 6). Collectively, these findings suggest that the incorporation of either TACE or HAIC, or both, into a systemic regimen with lenvatinib and camrelizumab offers comparable survival outcomes in this patient population.

Discussion

The present study highlighted the potential benefits of an integrated therapeutic approach for patients with HCC and PVTT, a subgroup traditionally associated with a poor prognosis (18). Despite advancements in systemic therapies for HCC, the specific challenges posed by PVTT require more nuanced treatment strategies. The results from the present study indicated that combination therapy of TACE-HAIC

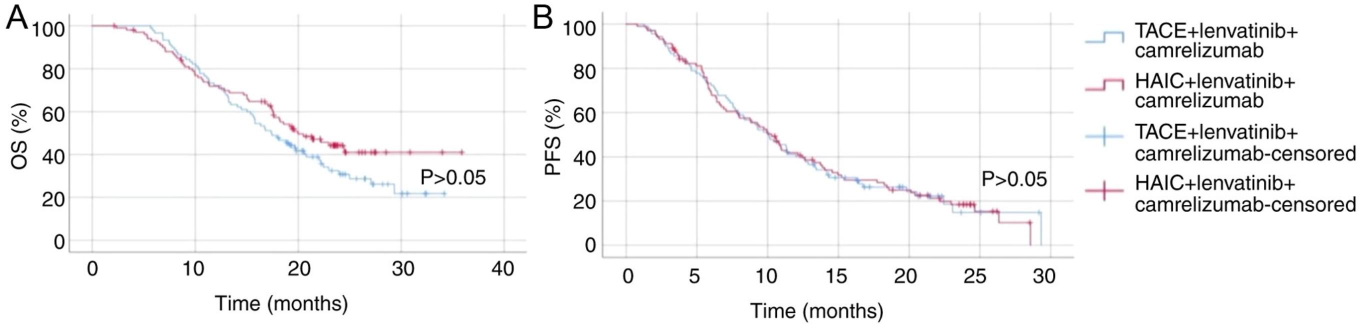

Figure 5. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between the patients with hepatocellular carcinoma treated with TACE + lenvatinib + camrelizumab (group 2) and those treated with HAIC + lenvatinib + camrelizumab (group 3). OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

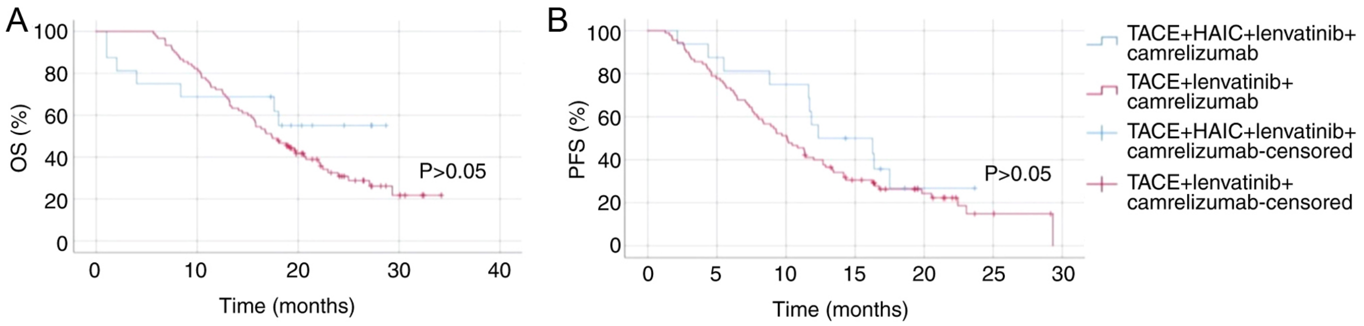

Figure 6. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between the patients with hepatocellular carcinoma treated with TACE + HAIC + lenvatinib + camrelizumab (group 1) and those treated with TACE + lenvatinib + camrelizumab (group 2). OS, overall survival; PFS, progression-free survival; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

with tyrosine kinase inhibitors (TKIs) and PD-1 inhibitors can significantly improve survival outcomes compared with TACE alone.

The enhanced efficacy of the combination therapy is evidenced by the markedly better survival metrics. For instance, patients treated with TACE-HAIC + lenvatinib + camrelizumab (group 1) exhibited significantly higher OS and PFS times compared with those treated with TACE alone (group 4), with P-values of 0.03 and 0.01, respectively. Additionally, group 2 (TACE + lenvatinib + camrelizumab) and group 3 (HAIC + lenvatinib + camrelizumab) both demonstrated improved OS and PFS times compared with group 4, with statistically significant differences (both $P<0.05$). Consistent with these findings, a number of previous studies have investigated both the effectiveness and the safety aspects of localized therapies (either TACE or HAIC individually) and their combination in treating HCC (22,23). The current research reinforces the effectiveness of combining TACE-HAIC, targeted therapy and immunotherapy for treating patients with HCC, particularly those with PVTT (24,25). These findings align with the hypothesis that an aggressive and multifaceted approach can be beneficial in this patient subset, corroborating earlier research that advocates for the use of multimodal therapies in advanced HCC with vascular invasion. Combination therapy in HCC with PVTT provides comprehensive antitumor effects. Primarily, chemotherapeutic agents trigger tumor cell apoptosis via jeopardizing DNA, alongside inducing immunogenic cell death. Such actions provoke a defensive antitumor immune reaction, thus boosting the potency of immunotherapy (26). Furthermore, TKIs harbor anti-proliferative and anti-angiogenic properties that effectively oppose hypoxia-driven angiogenesis via TACE-HAIC (27). Moreover, TKI therapy, when merged with anti-PD-1 treatment, has shown synergistic effects. This combination alters the immune environment of the tumor and enhances T cell penetration within it (28,29). In addition, anti-PD-1 treatment intensifies the ability of the immune system to combat tumors, thereby strengthening the overall immune assault on cancer cells (30,31). It should be noted that the lack of statistical significance between the quadruple and triple therapy groups may be due to the sample size.

The notable improvements in therapeutic outcomes must be balanced against the higher incidence of adverse events observed in the combination therapy group. While most events were manageable, the presence of adverse effects such as abdominal discomfort, diarrhea and appetite reduction in nearly all patients receiving combination therapy in the present study cannot be overlooked. This underscores the need for a careful selection of patients who are likely to tolerate and benefit from this intensive treatment regimen, considering the marked demands it places on patient quality of life.

While the current study presents promising results, it is imperative to acknowledge its limitations, including its retrospective nature and the relatively small sample size, which may influence the generalizability of the findings.

In conclusion, the present study successfully revealed that TACE-HAIC combined with lenvatinib and camrelizumab significantly improves both OS and PFS times in patients with HCC and PVTT compared with TACE alone, despite a higher incidence of adverse events. This combination therapy represents a promising treatment strategy for this patient population, offering enhanced survival benefits.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RL was responsible for conceptualization, methodology, resources, supervision and funding acquisition. DH was responsible for checking the data collection and follow-up data, writing (reviewing and editing), retrospective collection of clinopathological data and follow-up data aquisition and formal analysis. XH and QX checked the data collection and follow-up data, wrote the original draft and performed formal analysis. LY and HW were responsible for retrospective collection of clinopathological data and follow-up data aquisition, checking the data collection and follow-up data and writing (review and editing). JW and BL performed the retrospective collection of clinopathological data and follow-up data aquisition and formal analysis. XH and QX confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Harbin Medical University Cancer Hospital (Harbin, China; approval no. YD2024-11). The procedures used in this study were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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