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ORIGINAL RESEARCH

TACE-HAIC Plus Targeted Therapy and Immunotherapy for HCC with Tumor Thrombus and Arteriovenous Fistula

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Video abstract

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Objective: This study aimed to evaluate the clinical efficacy and safety of combined therapy (transcatheter arterial chemoembolization [TACE] with hepatic artery infusion chemotherapy [HAIC] combined with tyrosine kinase inhibitors [TKIs] and PD-1 inhibitors) versus TACE alone in hepatocellular carcinoma (HCC) patients with concurrent portal/hepatic vein tumor thrombus (PVTT/HVTT) and arteriovenous fistula (AVF).

Materials and Methods: This single-center retrospective study analyzed 301 HCC patients with PVTT/HVTT and AVF who received either combined therapy (n=177) or TACE monotherapy (n=124). Propensity score matching (PSM) was used to minimize confounding bias, yielding an average of 109 patients per group. Key outcomes compared included tumor thrombus regression rate, AVF closure rate, objective response rate (ORR), disease control rate (DCR), median overall survival (mOS), median progression-free survival (mPFS), and adverse events (AE).

Results: After PSM, the AVF complete closure rate of the combination therapy group was significantly higher than the TACE group (63.3% vs 27.5%, $p < 0.001$). According to response evaluation criteria in solid tumors (RECIST) 1.1 criteria for tumor thrombus response, the combination therapy group showed higher ORR (47.7% vs 7.3%, $p < 0.001$) and DCR (73.4% vs 50.5%, $p < 0.001$) than the TACE group. The combined therapy provided longer mOS (16.70 vs 10.40 months, $p < 0.0001$) and mPFS (14.23 vs 8.21 months, $p < 0.0001$) than TACE. The incidences of grade 3/4 AE were similar in both groups, respectively, 37.6% and 33.9%, $p = 0.57$.

Conclusion: Compared with TACE monotherapy, the combined therapy is a promising option with acceptable safety for HCC patients with PVTT/HVTT and AVF.

Keywords: combined therapy, hepatocellular carcinoma, portal vein tumor thrombus, hepatic arteriovenous fistula, hepatic vein tumor thrombus

Introduction

HCC ranks among the most lethal malignancies globally, with China bearing 45.2% of new cases and 47.1% of deaths worldwide.[1] Characterized by high vascular invasiveness, HCC frequently invades the hepatic portal and hepatic veins, forming venous tumour thrombus (VTT), among which the incidence of PVTT is the highest.[2] Approximately 10%-40% of patients have already presented with concurrent PVTT at the time of HCC diagnosis.[3] The tumor may also invade outflow tract vessels, causing HVTT. Hepatic arteriovenous fistula (HAVF)-pathological shunting between hepatic arteries and veins-occurs in 29%-63% of HCC cases.[4]

Critically, the co-existence of VTT and HAVF defines a distinct high-risk subgroup with a uniquely aggravated pathophysiology and dismal prognosis (mOS of 3–4 months without intervention).[5] The pathological mechanisms intertwine, creating a vicious cycle of mutual deterioration: VTT not only invades the adjacent venous system to directly

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induce or aggravate AVF, but also, in conjunction with the resulting AVF, creates a synergistic pathogenicity: VTT obstructs venous flow to exacerbate portal hypertension, while AVF diverts arterial flow, further elevating venous pressure and facilitating tumor dissemination and implantation. This dual pathology results in a clinical scenario far more complex than either condition alone, demanding tailored therapeutic strategies. The management of these patients represents a significant clinical dilemma, a challenge reflected in the latest BCLC 2025 strategy, which emphasizes the complexity of treating advanced HCC with complex vascular invasions and the need for tailored approaches.[6]

TACE remains a primary locoregional therapy for advanced HCC with vascular invasion in Asia[7] and shows therapeutic benefits for PVTT-associated cases.[8] However, AVF compromises TACE efficacy through embolic agent diversion, increasing risks of hepatic dysfunction, portal hypertension, and non-target embolization. This mechanistic is robustly supported by clinical evidence. Yasui et al explicitly addressed the issue of AVF, which causes suboptimal lipiodol deposition with conventional TACE (c-TACE) in HCC with PVTT and AVF. They reported that after combining with TACE-PVO to temporarily occlude the shunt, follow-up angiography confirmed AVF disappearance in 66.7% of cases. Crucially, in cases where AVF was eliminated, lipiodol accumulation improved to a near-complete or complete level in 100% of patients who had prior c-TACE.[9] While innovative, such technique is complex, high-risk, and not widely available, highlighting the persistent clinical dilemma posed by AVF. These illustrate a key treatment challenge specific to this subgroup: a standard therapy for VTT becomes potentially less effective and more hazardous.

In response to these limitations, combination strategies have emerged. Emerging evidence supports combining TACE-HAIC along with TKIs and PD-1 inhibitors significantly improves the mOS and mPFS compared to TACE monotherapy for HCC patients with VTT.[10] HAIC (FOLFOX regimen) delivers sustained high-dose chemotherapy to lesions inadequately embolized by TACE, particularly effective against PVTT.[11] Related study indicates that combining HAIC with TACE can further improve survival outcomes and ORR in unresectable HCC patients.[12] Furthermore, systemic therapy combining TKIs and PD-1 inhibitors has become integral to advanced HCC management, demonstrating significant survival benefits in landmark trials like Imbrave 150 and ORIENT-32.[13,14]

Recent studies have begun to explore combination strategies for this challenging cohort. For instance, a 2023 study by Lin et al directly compared HAIC (FOLFOX) combined with lenvatinib and PD-1 inhibitors versus TACE-based combination therapy in HCC patients with PVTT and AVF, demonstrating superior OS and PFS with the HAIC-based regimen.[15] This underscores the marked advantage of an HAIC-based approach and solidifies the potential of intensive combination therapy for this high-risk subgroup.

Despite these advancements, optimal management for this dual-pathology subgroup remains undefined, and a critical gap remains in the existing literature pertaining specifically to the subgroup. Current studies on combination therapies have predominantly focused on broad populations with vascular invasion, often stratifying results by VTT severity but seldom by the concomitant presence of AVF. More importantly, efficacy evaluations have largely centered on conventional endpoints like mOS and ORR. While crucial, these metrics are indirect measures that fail to quantify the reversal of the specific pathological mechanisms at play. Tumor thrombus, as a direct driver of portal hypertension and hepatic impairment, and AVF, with its shunting effect that exacerbates portal hypertension and facilitates metastasis, represent the core pathophysiology. Consequently, parameters such as tumor thrombus regression and AVF closure rate are vital as they directly determine restoration of portal hemodynamics, mitigation of severe complications, and feasibility of subsequent therapeutic interventions, yet they are consistently overlooked. This single-center retrospective study aims to comparatively analyze the efficacy and safety of combined therapy versus TACE monotherapy in HCC patients presenting with VTT and AVF.

Materials and Methods

Patient Selection

We conducted a retrospective analysis of 301 HCC patients with PVTT/HVTT and HAVF, treated at Harbin Medical University Cancer Hospital from January 2013 to December 2024.

Patients with venous tumor thrombus (PVTT or HVTT) were radiologically diagnosed based on preoperative imaging characteristics. PVTT extent was classified according to the Japanese Liver Cancer Study Group criteria (1987) as

follows: Vp1 (tumor thrombus confined to tertiary portal vein branches or smaller-caliber vessels), Vp2 (tumor thrombus extending to secondary portal vein branches), Vp3 (extending to first-order branches), and Vp4 (invading the main portal trunk or exceeding the hepatic hilum).[16]

HAVF were diagnosed through digital subtraction angiography (DSA) (Supplementary Figure 1–3) and were categorized into hepatic artery-portal vein fistula (HAPVF), hepatic artery-hepatic vein fistula (HAHVF), and mixed-type fistula (concurrent HAPVF and HAHVF) (Figure 1).

Based on the degree of shunt formation at the fistula opening, HAPVF severity is categorized angiographically as follows: (1) Mild: Opacification of fourth-order or smaller portal branches during the mid-arterial phase (> 3second); the "lipiodol portal sign" (visualization of peripheral portal branches following lipiodol emulsion injection) may be observed, though direct fistula morphology is typically occult; (2) Moderate: Second- or third-order portal branches opacified during the early-to-mid arterial phase (2–3 second); (3) Severe: Main portal trunk and primary branches opacified during the early arterial phase (< 2 second).[17] For HAHVF severity, classification is as follows: (1) Mild: Hepatic venous radicles opacified in the late arterial phase (> 3 second) with concealed fistula morphology; (2) Moderate: Hepatic veins and/or inferior vena cava opacified during the mid-arterial phase (2–3 second); (3) Severe: Hepatic veins and/or inferior vena cava opacified during the early arterial phase (< 2 second). Mixed type refers to simultaneous opacification of hepatic veins and portal veins during the arterial phase in DSA imaging.

Inclusion Criteria

(1) Age:18 to 75 years; (2) Confirmed HCC with PVTT/HVTT and HAVF; (3) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; (4) Child-Pugh class A or B; (5) White blood cell count > 3×10^9/L, neutrophil absolute count > 1.5×10^9/L, platelet count > 30×10^9/L, hemoglobin concentration > 85g/L; (6) Patients must have been treatment-naive for HCC prior to enrollment.

Exclusion Criteria

(1) Contraindications to Vascular Procedures: Absolute contraindications to angiography or arterial puncture; (2) Active Infection: Uncontrolled local infection adjacent to the target lesion or severe systemic infection; (3) Organ Dysfunction: Severe comorbidities involving the heart, lungs, or kidneys; (4) Oncologic History: History of secondary primary

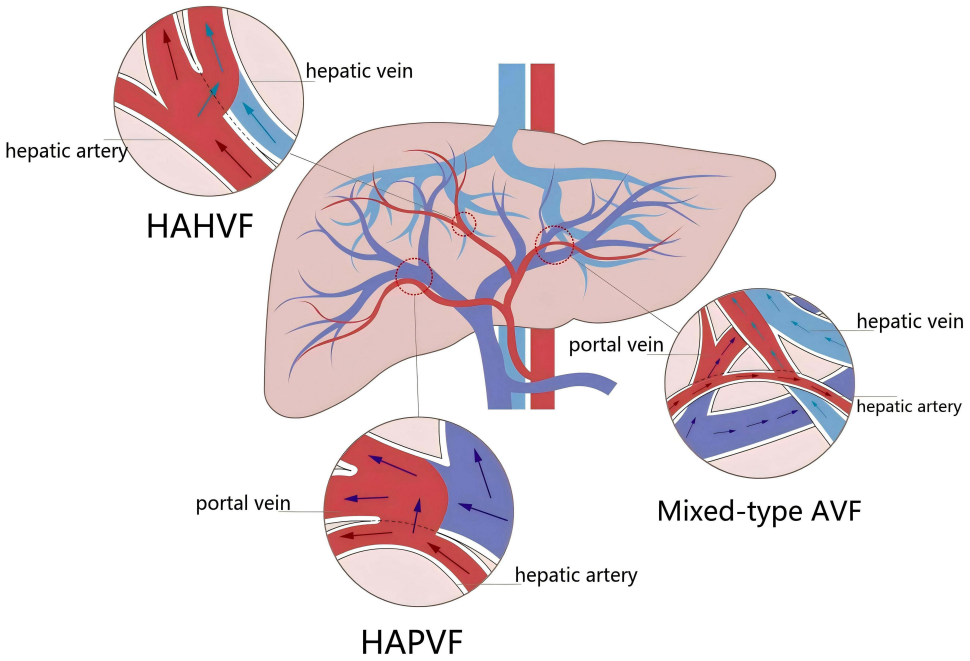

Figure 1 The illustrative classification of hepatic arteriovenous fistula.
Abbreviations: HAHVF, hepatic artery-hepatic vein fistula; HAPVF, hepatic artery-portal vein fistula; AVF, arteriovenous fistula.

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malignancy; (5) Data Integrity: Incomplete medical records or imaging data precluding adequate evaluation; (6) Compliance Issues: Inability to tolerate the procedure or adhere to follow-up protocols due to personal circumstances; (7) Loss to Follow-up.

Treatment Regimen

All TACE procedures employed the Seldinger technique via percutaneous femoral artery access. Following insertion of a 5F catheter sheath, guidewires and catheters were advanced under DSA fluoroscopic guidance. Selective catheterization was sequentially performed in the celiac trunk, proper hepatic artery, and superior mesenteric artery. High-pressure contrast injection facilitated angiographic identification of tumor-feeding vessels. When collateral circulation contributed to tumor vascularization, superselective angiography of collateral arteries was performed.

The embolization strategy depends on whether the microcatheter can cross the arteriovenous fistula opening: (1) If the microcatheter tip can pass through the fistula opening, embolization of tumor-feeding arteries distal to the fistula opening was prioritized to minimize non-target embolization. The catheter tip was then retracted to seal the fistula opening. After confirming successful closure, complete embolization of the tumor's feeding arteries was performed. (2) If the microcatheter tip was unable to cross the fistula opening, the fistula was first sealed before tumor-feeding arteries embolization treatment after comprehensively identifying the tumor's feeding vessels and the fistula site.

All TACE procedures performed in this study utilized cTACE methodology. The Iodized oil emulsion was prepared by thoroughly mixing 40 mg of epirubicin, 60 mg of cisplatin, and 5–10 mL of lipiodol, with the final lipiodol volume adjusted per patient based on tumor size and vascularity assessed on angiography. The fistula occlusion materials consist of calibrated microspheres, gelatin sponge particles, microcoils, and PVA particles. Pre-procedural superselective microcatheter angiography was mandatory to characterize the type, severity grade, and spatial architecture of the arteriovenous fistula. Embolic materials of varying diameters are then applied individually or in combination based on clinical needs and tailored to hemodynamic parameters. The frequency of TACE cycles for each patient is determined by clinical response and hepatic functional reserve, with intervals maintained at least 3–4 weeks apart.

The combination therapy group received TACE following the protocol described above. HAIC was administered as follows: a microcatheter was secured within the respective target vessel for infusion of FOLFOX-based chemotherapy via intra-arterial (IA). The specific regimen consisted of oxaliplatin (85 mg/m^2 over 2 hours), leucovorin (400 mg/m^2 over 2 hours), followed by 5-fluorouracil (5-FU) bolus (400 mg/m^2 over 1 hour) and continuous 5-FU infusion (2400 mg/m^2 over 23 hours). Combined TACE+HAIC sessions were repeated at 3–4-week intervals. Chemotherapeutic dosages could be appropriately adjusted based on the patient's general condition, body surface area (BSA), and tumor vascularity assessed by angiography.

In this study, PD-1 inhibitors (200 mg per agent) were administered intravenously starting on the first postoperative day and administered every 3 to 4 weeks, including sintilimab, tislelizumab, or camrelizumab. TKIs were initiated from the third postoperative day, with options including sorafenib (400mg orally twice daily), donafenib (400mg orally twice daily), and lenvatinib (8mg daily for <60kg patients; 12mg daily for ≥60kg patients). If Grade 3 or 4 treatment-related adverse events occurred, the dosages of sorafenib and donafenib were reduced to once daily, while lenvatinib was adjusted to 8mg daily (for ≥60kg patients) or 4mg daily (for <60kg patients). The selection of these PD-1 inhibitors and TKIs was determined by patient preferences, drug acquisition costs, and local health insurance reimbursement policies.

Assessment of Response

Due to the invasive nature of DSA, it is not suitable for follow-up examinations during non-interventional treatment phases. Therefore, the assessment of AVF status was exclusively based on DSA evaluations performed during each interventional procedure. The response of solid tumors and tumor thrombus was evaluated by contrast-enhanced CT or MRI 3–4 weeks after each interventional procedure. This systematic schedule enabled consistent serial assessment of anatomical and radiological changes. All imaging assessments were conducted independently by two experienced abdominal radiologists blinded to clinical data and treatment allocation, with any discrepancies resolved through consensus reading sessions to ensure maximum reliability and reproducibility of the radiological evaluations.

Tumor thrombus response was classified into the following categories based on tumor thrombus regression rate using RECIST 1.1 criteria:[18] Complete Response (CR) (complete disappearance of VTT), Partial Response (PR) (defined as ≥30% reduction in maximum diameter of the tumor thrombus relative to baseline measurements), Stable Disease (SD) (neither PR nor PD, reduction <30% or increase <20%), and Progressive Disease (PD) (defined as ≥20% increase in maximum diameter with an absolute growth ≥5 mm or new tumor thrombus detection).

For the overall tumor evaluation, the RECIST 1.1 was employed to quantify anatomical size changes, where target lesions were measured in their longest diameter with CR defined as disappearance of all target lesions, PR as ≥30% decrease in the sum of diameters relative to baseline, SD as neither sufficient shrinkage for PR nor sufficient increase for PD, and PD as ≥20% increase in the sum of diameters with an absolute increase of ≥5 mm or appearance of new lesions. Complementarily, the modified response evaluation criteria in solid tumors (mRECIST)[19] criteria specifically used for overall tumor assessment was applied to evaluate functional changes in tumor viability through arterial enhancement characteristics, where target lesions were measured in their maximum diameter of the tumor-enhanced area with CR indicating disappearance of any intratumoral arterial enhancement in all target lesions, PR as ≥30% decrease in the sum of viable diameters (enhancing portions), SD as neither PR nor PD, and PD as ≥20% increase in the sum of viable diameters with an absolute increase of ≥5 mm or appearance of new enhancing lesions.

AVF status was evaluated intraoperatively via DSA during each interventional procedure and categorized as follows: Complete closure: Total obliteration of AVF. Partial closure: Characterized by a delay in venous opacification time ≥1 second and/or a reduction in shunt vessel extent by ≥1 hierarchical level (eg, regression from main trunk to primary or secondary branches). Progression: Evidenced by advancement in venous opacification time ≥1 second and/or expansion of shunt vessels by ≥1 hierarchical level (eg, advancement from tertiary to secondary or primary branches). Stable: No significant change in AVF hemodynamics, with venous opacification time varying <1 second and no measurable alteration in shunt vessel extent. This classification system enabled standardized and reproducible assessment of AVF hemodynamic changes in response to therapy, with DSA serving as the gold standard for real-time evaluation during interventional sessions.

Follow-up and Safety Evaluation

Patients underwent pre-procedural evaluations including chest CT, contrast-enhanced abdominal CT or MRI, and relevant blood tests prior to each treatment cycle. Follow-up assessments were conducted approximately 3–4 weeks after each interventional therapy session, and subsequently at 3–6 week intervals until patient death or the end of the study (May 10, 2025). Each visit encompassed comprehensive clinical evaluation including medical history documentation, physical examination, chest CT, contrast-enhanced abdominal CT or MRI, and laboratory analyses comprising complete blood count, urinalysis, stool routine, hepatic and renal function panels, coagulation profiles, thyroid function tests, blood glucose levels, and tumor biomarkers.

Treatment-related AE were comprehensively assessed, encompassing all components of the therapeutic regimens. For patients in the TACE monotherapy group, AE related to the TACE procedure itself and its associated supportive care were captured. For patients in the combination therapy group, the safety monitoring extended to include AE potentially arising from HAIC, TKIs, and PD-1 inhibitors, in addition to those from TACE. This holistic approach ensured a complete evaluation of the safety profile for each therapeutic strategy. Treatment-related AE were prospectively monitored throughout follow-up and graded per the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0),[20] wherein Grade 1 denoted mild events requiring no intervention; Grade 2 indicated moderate events necessitating minimal intervention with limited instrumental activities appropriate for age of daily living; Grade 3 represented severe events prompting hospitalization or causing self-care impairment; Grade 4 signified life-threatening events demanding urgent intervention; and Grade 5 corresponded to AE-related mortality.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 29 and R 4.4.3 software. Baseline characteristics were compared based on variable types: categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, while continuous variables underwent normality assessment via the Shapiro–Wilk test, with normally distributed

data compared by independent samples *t*-test and non-normally distributed data analyzed via the Wilcoxon rank-sum test. PSM was implemented at a 1:1 ratio with a caliper width of 0.02, incorporating variables including sex, age, ECOG performance status, Child-Pugh grade, hepatitis history, liver cirrhosis, extrahepatic metastasis, tumor number, maximum tumor diameter, the extent of PVTT, hepatic vein tumor thrombus, AFP level, AVF type, AVF severity, ALT, AST, ALB, prothrombin time, platelet count, and white blood cell count. Balance between groups was assessed using standardised mean difference (SMD). An SMD below 0.1 indicates excellent balance, while an SMD below 0.2 is generally considered acceptable for indicating adequate balance after matching. Survival outcomes were estimated using the Kaplan-Meier method, and univariate/multivariate analyses were conducted via the Cox proportional hazards regression model to identify independent prognostic factors for overall survival (OS) and progression-free survival (PFS). All tests were two-sided, with $p < 0.05$ considered statistically significant.

Results

Patient Characteristics

Among these 301 patients included, 124 received TACE monotherapy, while 177 underwent combination therapy. The study protocol is presented in Figure 2. Before PSM, a significant disparity existed in the prevalence of extrahepatic metastasis between the two cohorts ($p < 0.014$). PSM was applied at a 1:1 ratio, yielding 109 matched pairs for comparative analysis. Post-PSM, all baseline characteristics were effectively balanced, with all SMD below 0.2 (indicating acceptable balance according to the absolute difference criterion) (Supplementary Figure 4), and all p-values greater than 0.05, as detailed in Table 1. The median follow-up duration was 18.00 months for the combination therapy group, during which patients received a median of 4.95 (range: 2.0–10.0) TACE-HAIC sessions; conversely, the TACE group exhibited a median follow-up of 15.08 months with 5.87 (range: 2.0–8.0) TACE treatments.

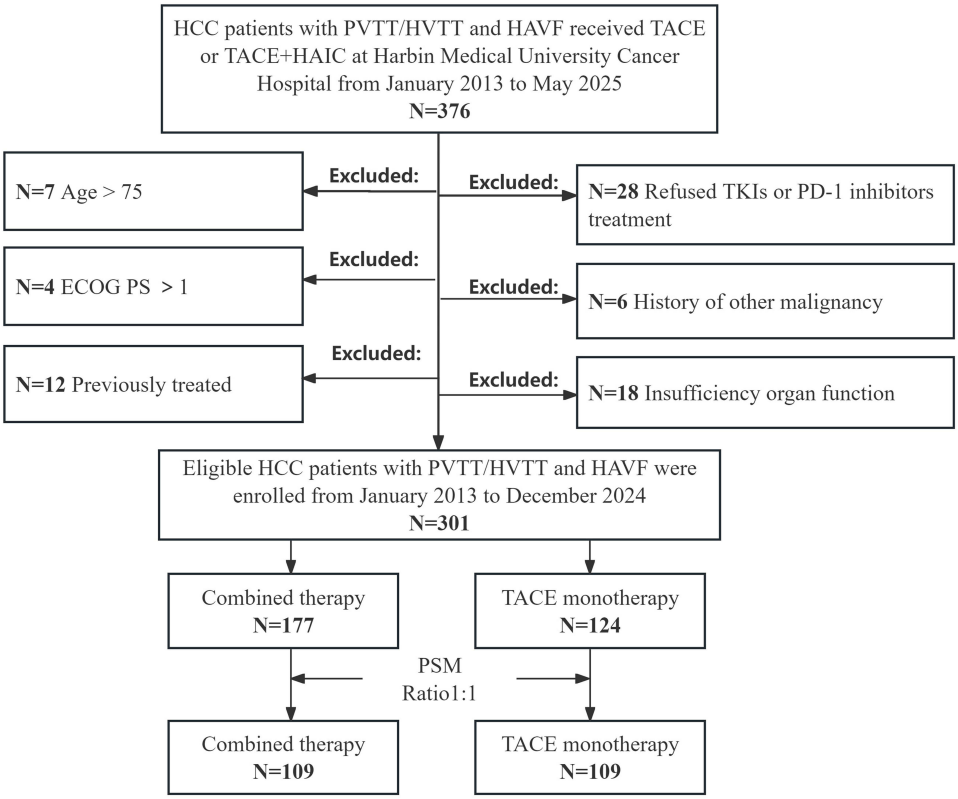

Figure 2 Flowchart of the study.

Abbreviations: HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; HAVF, hepatic arteriovenous fistula; TACE, transcatheter arterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; TKIs, tyrosine kinase inhibitors; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 1 Baseline Characteristics of the Patients

Characteristic	Before Matching		*p*	*SMD*	After matching		*p*	*SMD*
	TACE (n=124)	Combined Therapy (n=177)			TACE (n=109)	Combined Therapy (n=109)		
Age(years)	57 (52,63)	59 (52,65.5)	0.263	0.133	57 (52,63)	58 (51,63)	0.848	0.026
Sex			0.101	0.197			0.826	0.030
Male	113 (91.1)	150 (84.7)			98 (89.9)	97 (89)		
Female	11 (8.9)	27 (15.3)			11 (10.1)	12 (11)		
ECOG PS score			0.415	0.097			0.581	0.075
0	116 (93.5)	161 (91.2)			101 (92.7)	103 (94.5)		
1	8 (6.5)	16 (9.0)			8 (7.3)	6 (5.5)		
Child Pugh class			0.056	0.230			1.000	<0.001
A	112 (90.3)	146 (82.5)			97 (89)	97 (89)		
B	12 (9.7)	31 (17.5)			12 (11)	12 (11)		
Hepatitis			0.832	0.025			0.524	0.086
Yes	109 (87.9)	157 (88.7)			95 (87.2)	98 (89.9)		
No	15 (12.1)	20 (11.3)			14 (12.8)	11 (10.1)		
Cirrhosis			0.508	0.080			1.000	<0.001
Yes	123 (99.2)	174 (98.3)			108 (99.1)	108 (99.1)		
No	1 (0.8)	3 (1.7)			1 (0.9)	1 (0.9)		
Extrahepatic metastasis			0.014	0.301			1.000	<0.001
Yes	8 (6.5)	28 (15.8)			8 (7.3)	8 (7.3)		
No	116 (93.5)	149 (84.2)			101 (92.7)	101 (92.7)		
AFP level (ng/mL)			0.188	0.155			0.892	0.018
≥400ng/mL	57 (46)	95 (53.7)			51 (46.8)	50 (45.9)		
<400ng/mL	67 (54)	82 (46.3)			58 (53.2)	59 (54.1)		
ALT/(U/L)	43 (28.25,62)	41 (27,61.5)	0.613	0.130	39.8 (27,59.3)	40 (27.5,63)	0.697	0.129
AST/(U/L)	58.5 (41,86.75)	61 (43,94.5)	0.386	0.101	52 (38,80.5)	60 (44.5,104.5)	0.107	0.073
TBIL (umol/L)	19.55 (15.4,27.0)	21.5 (15.9,31.0)	0.167	0.152	19.8 (15.5,26.8)	20.39 (15.6,29.4)	0.654	0.013
ALB (g/L)	38.6 (35.3,42.2)	38.9 (35.8,42.6)	0.489	0.081	38.9 (35.9,42.5)	38.7 (36.2,42.7)	0.843	0.027
PT (s)	12.40 (11.7,13.3)	12.10 (11.60,13.1)	0.246	0.118	12.4 (11.7,13.3)	12.2 (11.6,13.1)	0.485	0.106
PLT(10^9/l)	135 (94.3,183.8)	152 (108.0,198.0)	0.066	0.090	139 (99.0,184.5)	152 (113.5,191.0)	0.315	0.005
WBC(10^9/l)	5.74 (4.5,7.3)	5.92 (4.7,7.4)	0.360	0.129	5.87 (4.5,7.5)	5.92 (4.7,7.3)	0.681	0.050
Solitary tumor			0.917	0.012			0.865	0.023
Yes	26 (21.0)	38 (21.5)			22 (20.2)	21 (19.3)		
No	98 (79.0)	139 (78.5)			87 (79.8)	88 (80.7)		
Largest tumor size(cm)			0.852	0.067			0.849	0.078
>10cm	60 (48.4)	82 (46.3)			54 (49.5)	53 (48.6)		
5-10cm	53 (42.7)	76 (42.9)			45 (41.3)	48 (51.6)		
<5cm	11 (8.9)	19 (10.7)			10 (9.2)	8 (7.3)		
PVTT classification			0.414	0.236			0.994	0.065
Vp0	15 (12.1)	22 (12.4)			12 (11.0)	12 (11.0)		
Vp1	11 (8.9)	15 (8.5)			11 (10.1)	9 (8.3)		
Vp2	18 (14.5)	40 (22.6)			18 (16.5)	18 (15.5)		
Vp3	48 (38.7)	54 (30.5)			39 (35.8)	40 (36.7)		
Vp4	32 (25.8)	46 (26.0)			29 (26.6)	30 (27.5)		
HVTT			0.931	0.020			1.000	<0.001
Yes	15 (12.1)	22 (12.4)			12 (11.0)	12 (11.0)		
No	109 (87.9)	155 (87.6)			97 (89.0)	97 (89.0)		
HAVF classification			0.985	0.020			0.495	0.161
HAPVF	87 (70.2)	124 (70.1)			77 (70.6)	84 (77.1)		
HAHVF	14 (11.3)	21 (11.9)			12 (11.0)	11 (10.1)		
Mixed-type	23 (18.5)	32 (18.1)			20 (18.3)	14 (12.8)		

(*Continued*)

Table 1 (Continued).

Characteristic	Before Matching		*p*	*SMD*	After matching		*p*	*SMD*
	TACE (n=124)	Combined Therapy (n=177)			TACE (n=109)	Combined Therapy (n=109)		
HAVF severity			0.627	0.114			0.809	0.088
Mild	14 (11.3)	20 (11.3)			14 (12.8)	11 (10.1)		
Moderate	29 (23.4)	50 (28.2)			25 (22.9)	25 (22.9)		
Severe	81 (65.3)	107 (60.5)			70 (64.2)	73 (67.0)		

Notes: Values are presented as n (%) or median (Q1, Q3). P values were calculated using a two-sidedχ2 test.
Abbreviations: TACE, transcatheter arterial chemoembolization; SMD, standardised mean difference; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet; WBC, white blood cell; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; HAVF, hepatic arteriovenous fistula; HAPVF, hepatic artery-portal vein fistula; HAHVF, hepatic artery-hepatic vein fistula.

Treatment Efficacy

After PSM, when evaluating tumor thrombus response using RECIST 1.1 criteria, the combination therapy group exhibited significantly higher ORR (47.7% vs 7.3%, $p < 0.001$), DCR (73.4% vs 50.5%, $p < 0.001$), and PR rate (45.0% vs 7.3%, $p < 0.001$) compared to the TACE group. Additionally, the AVF complete closure rate was markedly superior in the combination therapy group, with the AVF complete closure rate achieved in 63.3% versus 27.5% of the TACE group ($p < 0.001$) (Table 2).

Tumor response assessment by RECIST 1.1 criteria further confirmed the advantage of combined therapy for target lesions. The combination therapy group achieved higher ORR (45.9% vs 5.5%, $p < 0.001$), DCR (72.5% vs 47.7%, $p < 0.001$), and PR rate (45.9% vs 5.5%, $p < 0.001$) than the TACE group. Similarly, consistent outcomes were observed under mRECIST criteria: ORR (51.4% vs 9.2%, $p < 0.001$), DCR (73.4% vs 50.5%, $p < 0.001$), and PR rate (49.5% vs 9.2%, $p < 0.001$) all favored combined therapy (Table 2).

Survival Outcomes

At the end of follow-up, the mOS was 16.70 months (95% confidence interval [CI], 12.23–21.17) in the combination therapy group versus 10.40 months (95% CI, 9.72–11.08) in the TACE group ($p < 0.0001$) (Figure 3A). Univariate Cox regression analysis identified treatment modality (TACE monotherapy; hazard ratio [HR]: 0.31, 95% CI: 0.21–0.45, $p < 0.001$), PVTT classification (Vp3/4; HR: 1.62, 95% CI: 1.13–2.32, $p = 0.009$), and AVF severity (Severe; HR: 1.66, 95% CI: 1.15–2.40, $p = 0.007$) as independent risk factors for OS (Table 3). However, multivariate Cox regression analysis further revealed that only treatment modality (TACE monotherapy; HR 0.30, 95% CI: 0.21–0.44, $p < 0.001$) was the independent risk factor for OS (Table 3).

The mPFS was significantly prolonged in the combination therapy group (14.23 months; 95% CI: 10.40–18.06) compared to the TACE group (8.21 months; 95% CI: 7.56–8.86), $p < 0.0001$ (Figure 3B). The univariate analysis of factors affecting PFS revealed that treatment modality (TACE monotherapy; HR: 0.31, 95% CI: 0.22–0.44, $p < 0.001$), PVTT classification (Vp3/4; HR: 1.85, 95% CI: 1.30–2.64, $p < 0.001$), and AVF severity (Severe; HR: 1.83, 95% CI: 1.27–2.62, $p = 0.001$) were independent risk factors (Table 3). Multivariate analysis further confirmed treatment modality (TACE monotherapy; HR: 0.29, 95% CI: 0.20–0.41, $p < 0.001$) as the sole independent risk factor for PFS (Table 3).

To evaluate differences impact of PVTT subtypes and AVF severity on combined therapy efficacy and patient prognosis, stratified analyses were conducted within the combination therapy group. Given the exploratory nature of the following analyses and the sharply reduced sample sizes within subgroups, the results should be interpreted with caution. We compared OS and PFS between patients with different PVTT subtypes and AVF severity. Our findings indicated better prognosis for patients with Vp0-2 (n=39) in the combination therapy group compared to those with Vp3-4 (n=70) (Figures 3C and D). Similarly, patients with mild-to-moderate fistulas (n=36) showed superior survival outcomes than those with severe fistulas (n=73) within this group (Figures 3E and F). Consequently, we focused on

Table 2 Treatment Efficacy Evaluation of Tumor Thrombus, Overall Tumor and AVF

Response	RECIST 1.1 (Tumor Thrombus)		*p*	RECIST 1.1 (Overall Tumor)		*p*	mRECIST (Overall Tumor)		*p*	AVF status	Treatment Modality		*p*
	Combined Therapy	TACE		Combined Therapy	TACE		Combined Therapy	TACE			Combined Therapy	TACE	
ORR	52(47.7)	8(7.3)	<0.001	50(45.9)	6(5.5)	<0.001	56(51.4)	10(9.2)	<0.001	**Complete closure**	69(63.3)	30(27.5)	<0.001
DCR	80(73.4)	55(50.5)	<0.001	79(72.5)	52(47.7)	<0.001	80(73.4)	55(50.5)	<0.001	**Partial closure**	13(11.9)	21(19.3)	0.135
CR	3(2.8)	–	0.247	–	–	–	2(1.8)	0	0.498	**Stable**	16(14.7)	34(31.2)	0.004
PR	49(45.0)	8(7.3)	<0.001	50(45.9)	6(5.5)	<0.001	54(49.5)	10(9.2)	<0.001	**Progressive**	11(10.1)	24(22.0)	0.016
SD	28(25.7)	47(43.1)	0.007	29(26.6)	46(42.2)	0.015	24(22.0)	45(41.3)	0.002				
PD	29(26.6)	54(49.5)	<0.001	30(27.5)	57(52.3)	<0.001	29(26.6)	54(49.5)	<0.001				

Notes: Values are presented as n (%). P values were calculated using a two-sided $\chi 2$ test.

Abbreviations: AVF, arteriovenous fistula; RECIST, response evaluation criteria in solid tumours; mRECIST, modified response evaluation criteria in solid tumours; TACE, transcatheter arterial chemoembolization; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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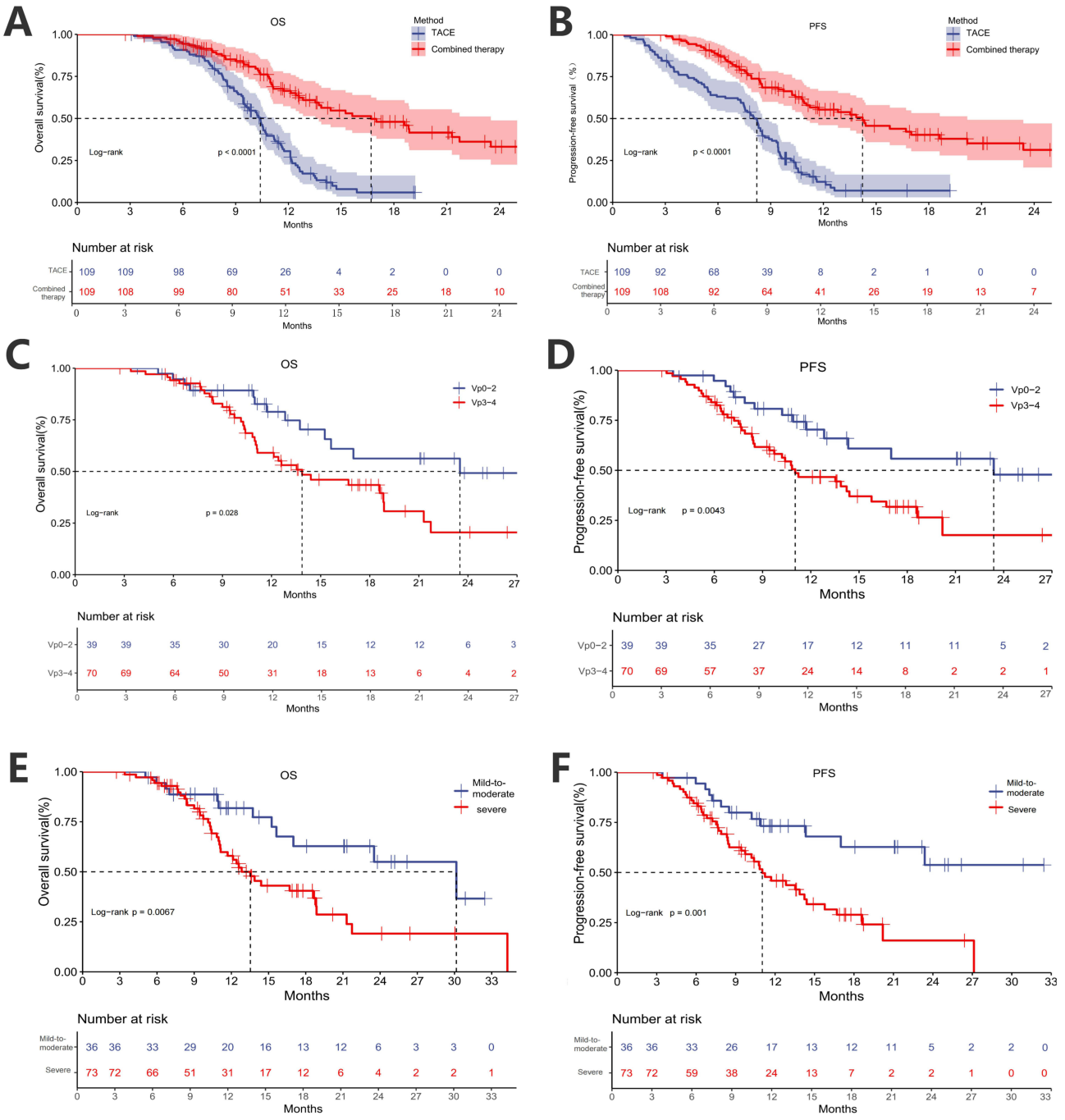

Figure 3 Kaplan–Meier survival curves comparing OS and PFS. (**A**) OS and (**B**) PFS of the patients who underwent combined therapy versus TACE after PSM. (**C**) OS and (**D**) PFS of the patients in combination therapy group with Vp0-2 versus Vp3-4. (**E**) OS and (**F**) PFS of the patients in combination therapy group with mild-to-moderate AVF versus severe AVF.

Abbreviations: OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; TACE, transcatheter arterial chemoembolization; AVF, arteriovenous fistula.

these high-risk subgroups to assess the therapeutic benefit of the combined strategy over TACE alone. Among patients with Vp3-4 PVTT, the combination therapy (n=70) conferred markedly superior survival benefits compared to TACE (n=68) (Figures 4A and B). Likewise, among patients with severe AVF, those receiving combination therapy (n=73) had significantly better outcomes than those receiving TACE (n=70) (Figures 4C and D).

The forest plot of multivariate Cox subgroup analysis demonstrated that compared with the TACE group, the combination therapy group exhibited a consistent trend toward lower risks of disease progression and mortality in

Table 3 Cox Regression Analyses of the Prognostic Factors for OS and PFS

Variables	OS Univariate		OS Multivariate		PFS Univariate		PFS Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Treatment modality								
Combined therapy/TACE	0.311(0.214–0.452)	<0.001	0.299(0.205–0.437)	<0.001	0.309(0.217–0.442)	<0.001	0.286(0.199–0.412)	<0.001
Sex								
Male/Female	1.533(0.864–2.721)	0.144			1.049(0.615–1.782)	0.860		
Age(years)								
<65/≥65	1.305(0.861–1.978)	0.210			1.250(0.832–1.879)	0.282		
ECOG PS score								
0/1	1.165(0.629–2.159)	0.627			1.087(0.588–2.010)	0.790		
Child Pugh class								
A/B	0.969(0.565–1.662)	0.909			1.047(0.621–1.768)	0.862		
Hepatitis								
Yes/No	0.771(0.469–1.266)	0.304			0.843(0.508–1.398)	0.507		
Cirrhosis								
Yes/No	2.484(0.346–17.80)	0.365			0.928(0.229–3.756)	0.916		
Extrahepatic metastasis								
Yes/No	1.103(0.596–2.044)	0.754			1.114(0.617–2.011)	0.720		
AFP level(ng/mL)								
≤400/>400	1.180(0.843–1.650)	0.334			0.986(0.715–1.360)	0.932		
Solitary tumor								
Yes/No	1.322(0.838–2.087)	0.231			1.208(0.791–1.846)	0.382		
Largest tumor size(cm)								
≤10/>10	0.949(0.679–1.325)	0.757			0.986(0.715–1.360)	0.932		
PVTT classification								
Vp0-2/ Vp3-4	1.615(1.126–2.317)	0.009	1.473(0.622–3.491)	0.378	1.853(1.302–2.637)	<0.001	2.104(0.881–5.021)	0.094
HVTT								
Yes/No	0.850(0.497–1.455)	0.554			0.756(0.443–1.289)	0.304		
HAVF classification								
HAPVF/HAHVF&Mixed-type	1.199(0.834–1.724)	0.327			1.047(0.732–1.496)	0.802		
HAVF severity								
Mild-to-moderate/Severe	1.663(1.150–2.404)	0.007	1.211(0.503–2.914)	0.670	1.826(1.273–2.619)	0.001	1.022(0.421–2.481)	0.962
ALT (U/L)	0.999(0.997–1.002)	0.597			0.999(0.997–1.002)	0.574		
AST (U/L)	1.000(0.999–1.002)	0.574			1.001(0.999–1.002)	0.371		
TBIL (umol/L)	1.009(0.996–1.021)	0.166			1.010(0.996–1.024)	0.133		
ALB (g/L)	0.972(0.939–1.006)	0.104			0.964(0.932–0.997)	0.032		
PT (s)	1.061(0.922–1.220)	0.408			1.087(0.948–1.247)	0.231		
PLT (10^9/L)	0.999(1.001–1.003)	0.521			1.000(0.998–1.003)	0.670		
WBC (10^9/L)	1.048(0.979–1.122)	0.177			0.993(0.928–1.063)	0.850		

Notes: Analyses were performed using Cox proportional hazard regression model.

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; HAVF, hepatic arteriovenous fistula; HAPVF, hepatic artery-portal vein fistula; HAHVF, hepatic artery-hepatic vein fistula; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PLT, platelet; WBC, white blood cell.

nearly all subgroups. To further validate the homogeneity of therapeutic efficacy, we performed interaction tests between treatment modalities and baseline stratification factors (including PVTT classification and AVF severity). The results demonstrated no significant interaction effects (all $P > 0.05$). This finding, consistent with the multivariate Cox subgroup analysis presented in the forest plot, confirms the consistent treatment benefit of combined therapy across these subgroups (Figures 5A and B).

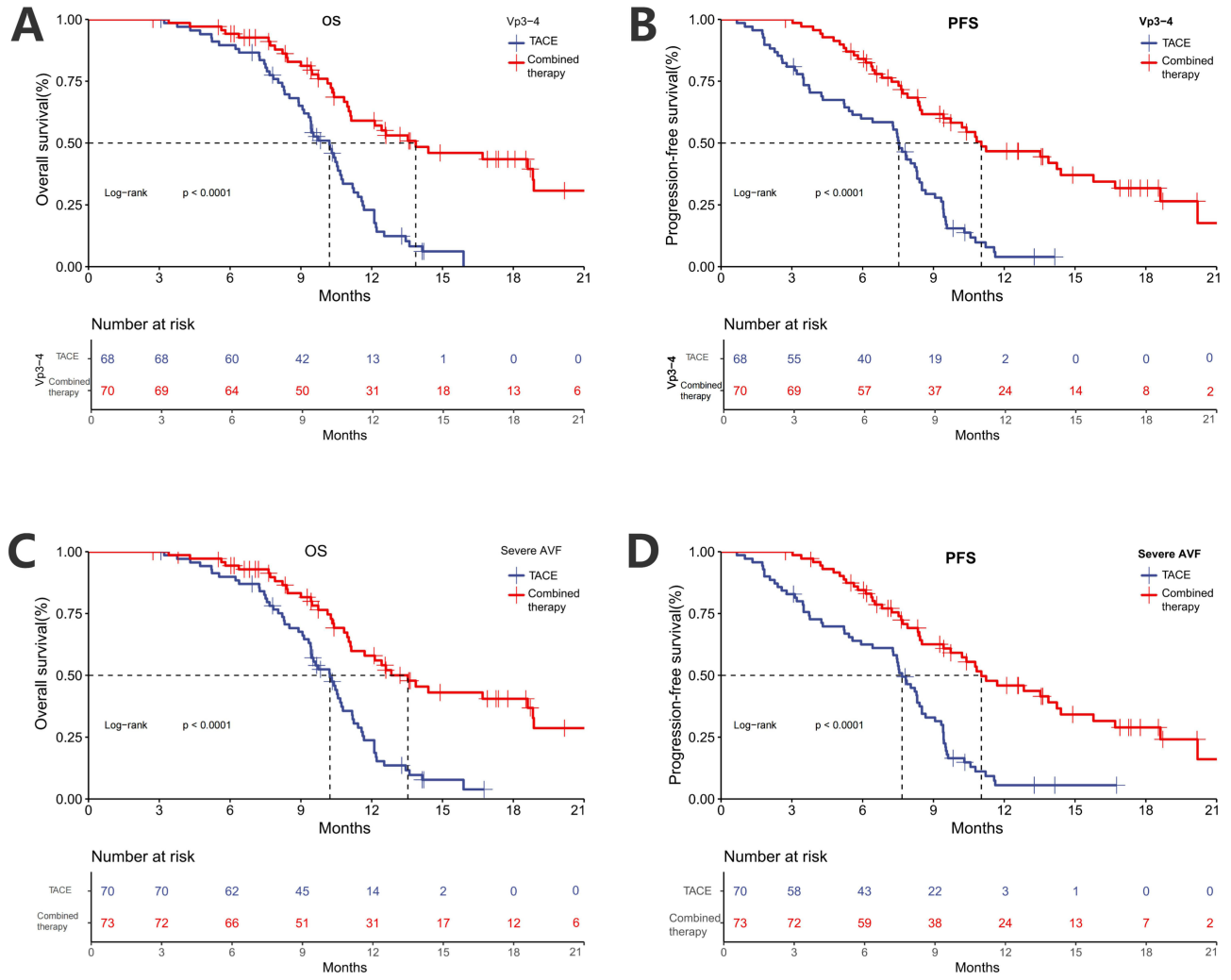

Figure 4 Kaplan–Meier survival curves comparing OS and PFS. (**A**) OS and (**B**) PFS of the patients with Vp3-4 who underwent combined therapy versus TACE. (**C**) OS and (**D**) PFS of the patients with severe AVF who underwent combined therapy versus TACE.
Abbreviations: OS, overall survival; PFS, progression-free survival; TACE, transcatheter arterial chemoembolization; AVF, arteriovenous fistula.

Treatment Safety

In this study, compared to the TACE monotherapy cohort, the combined therapy cohort demonstrated higher incidences of elevated alanine aminotransferase (ALT) (80.7% vs 56.9%, $p < 0.001$), elevated aspartate aminotransferase (AST) (77.1% vs 56.0%, $p < 0.001$), hyperbilirubinemia (67.0% vs 45.9%, $p = 0.002$), hypertension (22.9% vs 10.1%, $p = 0.011$), hypoalbuminemia (32.1% vs 11.9%, $p < 0.001$), and thrombocytopenia (28.4% vs 5.5%, $p < 0.001$). However, the overall incidence of treatment-related AE was comparable between two groups (Table 4), with no treatment-related mortality observed. Crucially, no statistically significant difference was identified in the rates of grade 3/4 AE (37.6% vs 33.9%, $p = 0.57$), indicating that the combined therapy regimen did not exacerbate severe toxicities despite its enhanced efficacy profile.

Discussion

Our retrospective study demonstrates that for HCC patients with VTT and AVF, combined therapy significantly outperforms TACE monotherapy, achieving higher AVF closure rate, tumor thrombus regression rate, mOS, mPFS, and ORR. Despite these promising results, the optimal therapeutic strategy for this high-risk subgroup remains inconclusive. Recent years have witnessed the development of a multimodal strategy combining local interventional therapy with systemic

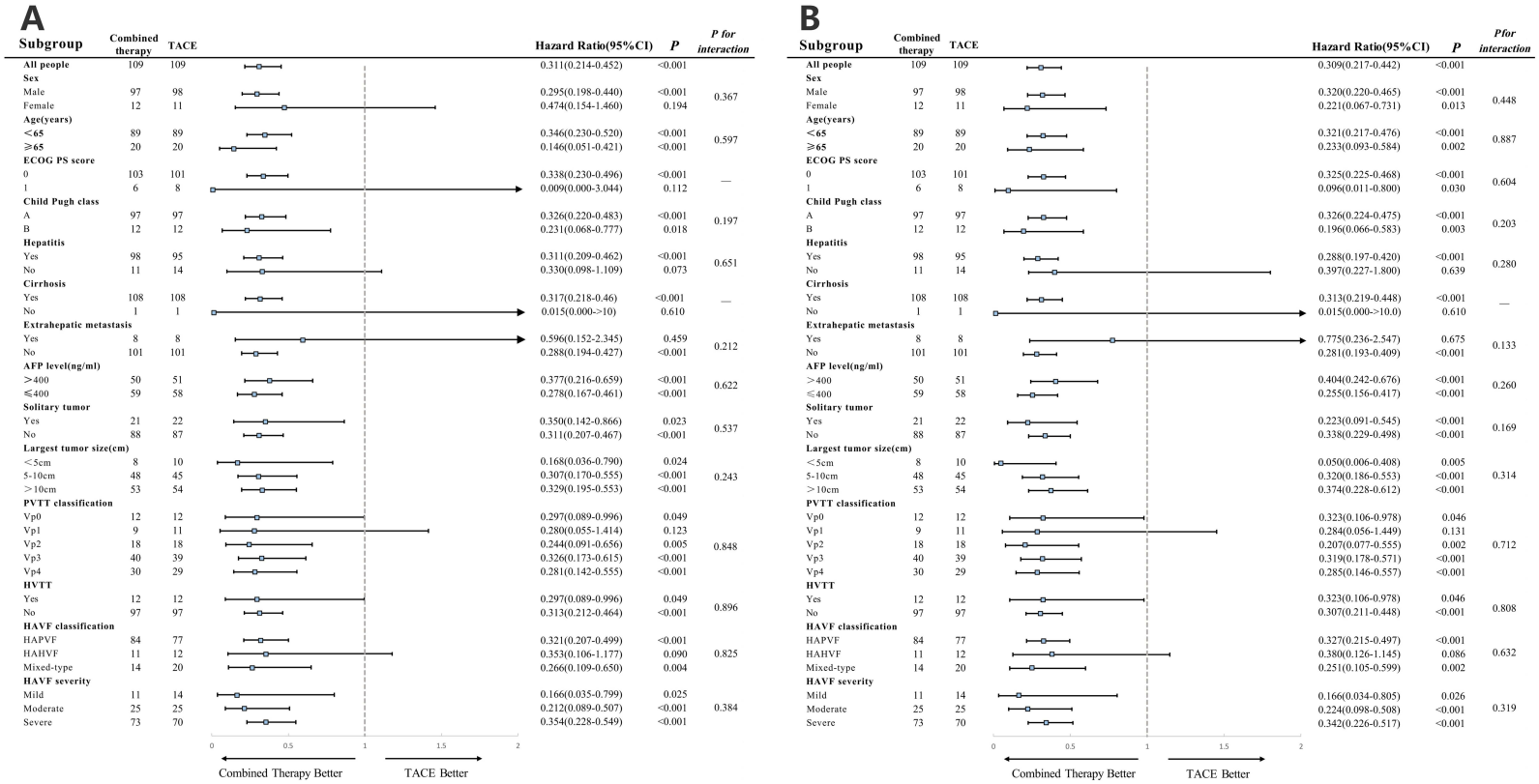

Figure 5 Subgroup analyses of OS (**A**) and PFS (**B**).

Abbreviations: OS, overall survival; PFS, progression-free survival; CI, confidence interval; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; HAVF, hepatic arteriovenous fistula; HAPVF, hepatic artery-portal vein fistula; HAHVF, hepatic artery-hepatic vein fistula.

Table 4 Treatment-Related Adverse Events

Adverse Events	Any Grade		*p*	Grade≥3		*p*
	Combined Therapy (n=109)	TACE (n=109)		Combined Therapy (n=109)	TACE (n=109)	
Total	106(97.25)	105(96.33)	0.701	41(37.61)	37(33.94)	0.572
Elevated ALT	88(80.73)	62(56.88)	<0.001	19(17.43)	17(15.60)	0.715
Elevated AST	84(77.06)	61(55.96)	<0.001	18(16.51)	15(13.76)	0.571
Hyperbilirubinemia	73(66.97)	50(45.87)	0.002	16(14.68)	14(12.84)	0.694
Abdominal distension	21(19.27)	19(17.43)	0.726	11(10.09)	10(9.17)	0.818
Diarrhea	20(18.35)	16(14.68)	0.466	7(6.42)	4(3.67)	0.353
Nausea/vomiting	22(20.18)	27(24.77)	0.417	8(7.34)	14(12.84)	0.177
Hand-foot syndrome	15(13.76)	-	-	7(6.42)	-	-
Gastrointestinal hemorrhage	4(3.67)	3(2.75)	0.701	1(0.92)	1(0.92)	1.000
Abdominal pain	39(35.78)	27(24.77)	0.077	15(13.76)	13(11.93)	0.686
Decreased appetite	9(8.26)	6(5.50)	0.422	-	-	-
Rash	17(15.60)	-	-	8(7.34)	-	-
Weight decreased	18(16.51)	14(12.84)	0.444	-	-	-
Hypertension	25(22.94)	11(10.09)	0.011	7(6.42)	6(5.50)	
Fever	23(21.10)	18(16.51)	0.386	-	-	-
Leukopenia	11(10.09)	9(8.26)	0.639	6(5.50)	4(3.67)	0.775
Hypoalbuminemia	35(32.11)	13(11.93)	<0.001	9(8.26)	5(4.59)	0.269
Thrombocytopenia	31(28.44)	6(5.50)	<0.001	4(3.67)	1(0.92)	0.175

Notes: Values are presented as n (%). P values were calculated using a two-sided $\chi 2$ test.
Abbreviations: TACE, transcatheter arterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

treatment to enhance efficacy in intermediate-to-advanced HCC synergistically. This is supported by a systematic review by Wang et al, which analyzed therapies for HCC with vascular invasion (eg, HVTT) and concluded that combined local and systemic strategies provide superior long-term survival with manageable complications compared to surgery with adjuvant therapy.[21] Consistent with this, in a pivotal study evaluating quadruple therapy (TACE + HAIC + targeted therapy + immunotherapy) in intermediate-to-advanced HCC, the combination group achieved markedly higher ORR and DCR of 80% and 94%, respectively, significantly surpassing the 41.2% (ORR) and 74.5% (DCR) observed in the TACE monotherapy group.[22] Notably, the multicenter retrospective GUIDANCE-001 study demonstrated that TACE combined with targeted therapy and immunotherapy versus TACE alone generated a statistically significant prolongation of mPFS by 7.9 months (15.9 months vs 8.0 months; $p < 0.001$) and improved OS, alongside elevated rates of surgical conversion and pathological complete response in intermediate-to-advanced HCC patients.[23] Furthermore, the Phase III LAUNCH trial corroborated that lenvatinib combined with TACE yielded substantially prolonged OS, PFS, and elevated ORR compared to lenvatinib monotherapy in advanced HCC cohorts.[24]

TACE, while a mainstay for unresectable HCC, exhibits significant limitations when applied to patients concurrently presenting with PVTT (or HVTT) and HAVF. VTT (PVTT or HVTT) receives dual blood supply from both hepatic arterial and portal or hepatic venous systems; conventional TACE only embolizes the hepatic artery or its branches, failing to disrupt nutritional support from portal or hepatic veins to the tumor thrombus, thereby enabling proliferation of viable residual cancer cells and driving disease progression. Additionally, post-embolization hypoxia activates hypoxia-inducible factor-1α (HIF-1α), triggering upregulation of pro-angiogenic genes (eg, VEGF, matrix metalloproteinases [MMPs]), which enhances cancer cell invasiveness and metastatic potential.[25] Studies have corroborated that the expression level of vascular endothelial growth factor (VEGF) in residual tumor tissue was significantly higher after TACE compared to before the procedure.[26] In the context of concomitant AVF, embolic agents may migrate through fistulous tracts into non-target vasculature, precipitating life-threatening complications such as non-target embolization or even pulmonary embolism. Concurrently, HAVF can also lead to embolic agent leakage, reducing local drug

concentration and compromising local therapeutic efficacy. Consequently, TACE monotherapy not only fails to inhibit the tumor growth but may even promote intrahepatic and extrahepatic metastasis. Repeated TACE sessions under these conditions exacerbate hepatic functional impairment, further diminishing patient fitness for subsequent interventions. Clinical studies have substantiated the limitations of TACE monotherapy in Vp3/4 patients, demonstrating poor treatment outcomes: TACE monotherapy showed no efficacy in Vp4 patients;[27] The complete response rate was 0%, the partial response rates ranged from 19.5% to 26.3% and the median overall survival for Vp3/4 patients was merely 5.2 months.[28]

HAIC delivers high-concentration chemotherapeutic agents through continuous infusion, effectively targeting collateral circulation and microscopic metastases unembolized by TACE. The drug concentration in the intratumoral area is markedly higher than that in the systemic circulation. This pharmacokinetic advantage significantly enhances drug penetration into tumor thrombus, thereby promoting necrosis and regression of both tumor and tumor thrombus.[29] In combination with TACE, embolic agents such as gelatin sponge particles are used to physically occlude the fistula preemptively, reducing abnormal diversion of chemotherapeutic and embolic agents, and controlling tumors more safely and effectively. HAIC exhibits particularly significant efficacy in HCC patients with PVTT. A multicenter retrospective cohort study revealed that compared to the lenvatinib + TACE cohort, the lenvatinib + TACE + HAIC cohort achieved superior ORR, longer time to progression (TTP), and improved OS in treating HCC with PVTT ($P < 0.001$).[11] Moreover, the Japanese Society for Hepatology (JSH) has directly endorsed HAIC as a standard therapy for HCC patients complicated by PVTT.[30]

Molecular targeted agents inhibit tyrosine kinase receptors such as VEGFR and PDGFR, directly suppressing vascular endothelial cell proliferation and reducing the neovascularization nourishing tumor thrombus. Simultaneously, these agents block downstream signaling pathways, including RAS/MAPK and PI3K/AKT, thereby decreasing tumor cell invasiveness and lowering the risk of intrahepatic metastasis. For patients with HVTT, targeted therapy inhibits thrombus dissemination along hepatic veins into the inferior vena cava or even right atrium, thereby preventing severe complications such as Budd-Chiari syndrome and pulmonary embolism. In cases complicated by HAVF, these agents suppress vascular endothelial growth factor (VEGF) and its receptors, reducing aberrant perifistular tumor angiogenesis and promoting indirect fibrotic occlusion of fistulous tracts.[31]

Immunotherapy activates or enhances the patient's immune system to recognize and eliminate cancer cell. These agents reverse tumor-induced immunosuppression by restoring T-cell reactivity, enabling them to recognize and attack cancer cell while activating systemic immune responses to control extrahepatic micrometastases.[32] In fact, most HCC patients exhibit a "cold" tumor immune microenvironment (TME), which renders immunotherapy largely ineffective. Studies demonstrate that TACE promotes the release of tumor-associated antigens and enhances antigen availability, thereby activating dendritic cell and facilitating T-cell activation and proliferation. This process prepares the immune system for antitumor responses. Furthermore, the release of damage-associated molecular patterns (DAMPs) during tumor cell death further amplifies immunogenic signaling, thereby establishing a robust antitumor immune cascade. In summary, TACE ultimately converts the TME from an immunoresponsive "cold" state to an immunoresponsive "hot" state.[33] Not only is VEGF a proangiogenic factor, but it also plays a crucial role in fostering an immunosuppressive TME by inhibiting dendritic cell function and inducing myeloid-derived suppressor cells (MDSCs) to indirectly exhaust T-cell.[34] Consequently, molecular targeted agents not only normalize tumor vasculature but also alleviate VEGF-mediated immunosuppression, thereby improving the immune cell infiltration. Meanwhile, immunotherapeutic agents further amplify T-cell cytotoxicity and synergize with the immunomodulatory effects of molecular targeted agents, thereby establishing an immune-related synergistic amplification path characterized by "vascular normalization → enhanced immune infiltration → amplified antitumor immunity → potentiated tumor cytotoxicity".

The superior clinical outcomes observed with the combination therapy may be rooted in its potential to induce a potent, coordinated form of immunogenic cell death, potentially aligning with the novel paradigm of PANoptosis. As elaborated by Xiang et al (2025), PANoptosis represents an integrated inflammatory cell death pathway orchestrated by the PANoptosome complex, which simultaneously engages key components of pyroptosis, apoptosis, and necroptosis.[35] This unique configuration is particularly relevant to our multimodal regimen: the substantial cellular stress and direct cytotoxicity induced by TACE-HAIC and targeted agents (TKIs) could serve as a potent trigger for PANoptosis. This would result in the robust release of DAMPs and pro-inflammatory cytokines (eg, IL-1β, IL-18), thereby creating

a favorable immunogenic microenvironment.[36] This process provides a mechanistic substrate for the observed TME reprogramming from "cold" to "hot," as it potently promotes dendritic cell maturation and recruitment of cytotoxic T cells and NK cells. Furthermore, the synergy between targeted therapy and immunotherapy finds a plausible explanation in this model, as evidence suggests that TKIs like sorafenib can directly activate the PANoptotic pathway, which in turn sensitizes tumors to PD-1 checkpoint blockade.[37] Thus, the PANoptosis framework offers a unifying molecular perspective that helps explain the enhanced efficacy of our combination strategy, particularly in this challenging subgroup with complex vascular pathologies, by linking intensive tumor cell killing to robust, synergistic anti-tumor immunity. The synergistic effects among these therapies provide a robust theoretical foundation for combination strategies.

Therefore, this study combined locoregional and systemic therapies to overcome their respective limitations. Our previous study aligns with and reinforces the core findings of this study,[38] which confirmed that TACE-HAIC plus targeted therapy and immunotherapy yields superior outcomes compared to TACE alone. However, this research extends the evidence base by focusing on a more challenging and understudied subgroup. While prior work primarily addressed PVTT, our introduction of novel endpoints—such as tumor thrombus regression rate and AVF closure rate—alongside survival metrics, provides a more granular evaluation of therapeutic efficacy, highlighting the unique ability of combination therapy to reverse critical pathological processes in this high-risk population. PSM was employed to minimize confounding biases and reduce intergroup disparities, thereby enhancing the reliability of outcomes. Thus, our study not only corroborates the benefits of multimodal approaches but also delineates their enhanced applicability in complex scenarios involving dual vascular complications. Results demonstrated significantly superior outcomes in the combination therapy group compared to the TACE group, including tumor thrombus regression rate, arteriovenous fistula closure rate, and survival benefits (mOS and mPFS). Furthermore, we investigated whether therapeutic efficacy correlated with the severity of tumor thrombus or AVF. Subgroup analysis revealed that patients with Vp3-4 or severe fistulas exhibited poorer prognoses relative to those with Vp0-2 or mild-to-moderate fistulas. Nevertheless, when these high-risk subgroups were further compared with TACE-treated Vp3-4 and severe fistula patients, the combination therapy still provided significantly longer OS and PFS than TACE monotherapy. To further validate the homogeneity of treatment effects, we conducted interaction tests to assess whether the efficacy of combination therapy varied significantly across key subgroups, including PVTT classification and AVF severity. The interaction analyses yielded non-significant P values (all $P > 0.05$), indicating no evidence of differential treatment effects based on these factors. This reinforces that the survival benefit of combination therapy was consistent regardless of baseline tumor thrombus or fistula characteristics. This finding offers a promising therapeutic strategy for advanced HCC patients with venous tumor thrombus (PVTT or HVTT) and HAVF.

In HCC complicated by venous tumor thrombus, the nourishing vessels within the venous wall undergo pathological dilation and hypertrophy, becoming the primary feeding arteries. Alternatively, tumor invasion into adjacent venous branches directly establishes arteriovenous communications. Both scenarios result in direct shunting of hepatic arterial flow into the venous system, thereby forming the HAVF.[39] Consequently, such HAVF frequently arise secondary to tumor thrombus, while simultaneously serving as conduits for tumor cell dissemination and direct diversion of arterial blood into the venous system.This hemodynamic shift precipitates an abrupt increase in venous system pressure and reduction in flow velocity, creating a permissive microenvironment for tumor cell adhesion and thrombus dissemination. Thus, tumor thrombus and arteriovenous fistula exhibit a reciprocal causal relationship, collectively exacerbating patient prognosis and survival outcomes. Tumor thrombus represents an invasive hallmark of malignancy, directly contributing to portal hypertension, hepatic function impairment, and potential liver failure. Simultaneously, the shunting effect induced by AVF further exacerbates portal hypertension, causes loss of TACE embolic agents, and facilitates intrahepatic/extrabepatic tumor metastasis. Conventional endpoints such as OS and PFS fail to quantify these specific pathological alterations. In contrast, tumor thrombus regression rate combined with AVF closure rate directly reflects the therapeutic reversal of core pathological mechanisms. Therefore, we prioritized evaluating tumor thrombus regression rate and AVF closure rate as dual endpoints, deconstructing the clinical response to combination therapy into antitumor effects (tumor thrombus regression) and vascular remodeling effects (AVF closure).

Our study has several limitations that warrant acknowledgment. First, the retrospective, single-center design inherently introduces risks of selection bias and unmeasured confounding, despite the use of propensity score matching. The

absence of an independent external validation cohort remains a critical constraint, potentially limiting the generalizability of our findings. Second, key prognostic confounders, such as patient adherence to oral targeted agents and immunotherapies, as well as the prognostic impact of baseline comorbidities, were not systematically assessed. This omission may influence the accurate interpretation of survival outcomes. Third, although the sample size is substantial for this specific high-risk population, it remains relatively modest for extensive stratification. The sharp drop in reduced sample sizes in the exploratory subgroup analyses increases the risk of false-positive findings. Furthermore, the analysis of HVTT was constrained by the absence of a universally accepted grading system and the limited sample size, which precluded a meaningful subgroup analysis based on HVTT extent. Therefore, we focused on HVTT as a dichotomous variable (present or absent) to ensure analytical robustness. Finally, the median follow-up duration, particularly for the combination therapy group, was still short, necessitating further studies with extended follow-up to validate the long-term efficacy and safety. Future multi-center, larger prospective randomised controlled trials incorporating comprehensive comorbidity and medication adherence assessments are required to overcome these limitations and confirm our conclusions. Nevertheless, our current experimental results provide valuable clues for subsequent research.

In conclusion, this retrospective study suggests that, for HCC patients with PVTT/HVTT and AVF, the combined therapy may be a promising therapeutic option associated with improved survival outcomes and an acceptable safety profile when compared to TACE monotherapy. These findings, while encouraging, require validation in prospective studies to account for potential biases inherent in the retrospective design.

Data Sharing Statement

The datasets associated with the article used or analyzed to support these results are available from the corresponding author upon reasonable request.

Ethical Approval

The study conformed to the ethical guidelines of the 1989 Declaration of Helsinki and was approved by the Ethics Committee of Harbin Medical University Cancer Hospital (Harbin, China; approval no. 2024-428-IIT).

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Consent to Participate

Written informed consent was obtained from all patients.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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