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Comparison of HAIC plus Targeted Immunotherapy and TACE plus Targeted Immunotherapy in Unresectable BCLC Stage C Hepatocellular Carcinoma with Up-to-11 High Tumor Burden: A Multicenter Retrospective Study

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Research Article

Keywords: Hepatocellular carcinoma, Hepatic artery infusion chemotherapy, Transarterial chemoembolization, Tumor burden, Targeted immunotherapy

Posted Date: July 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9990068/v1

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Additional Declarations: No competing interests reported.

Abstract

Objective

This study aimed to compare the efficacy and safety of hepatic arterial infusion chemotherapy (HAIC) plus targeted immunotherapy (TI) versus transarterial chemoembolization (TACE) plus TI in unresectable BCLC stage C hepatocellular carcinoma (HCC) patients with high tumor burden who met the Up-to-11 criterion (total tumor number plus maximum diameter > 11).

Methods

We retrospectively enrolled consecutive patients with unresectable BCLC stage C HCC who met the Up-to-11 criterion from six tertiary hospitals in China between January 2020 and June 2024. All patients received HAIC + TI (HTI group) or TACE + TI (TTI group) as first-line locoregional combined systemic therapy. A 1:1 propensity score matching (PSM) was performed to balance baseline characteristics. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and treatment-related adverse events (AEs).

Results

Overall, 175 eligible patients were initially recruited, including 63 in the HTI group and 112 in the TTI group. After 1:1 PSM, 46 patients remained in each cohort, with a median follow-up of 15.0 months (IQR, 9.0-23.6 months). Post-matching median OS was comparable between the two groups (18.0 months vs 16.3 months, HR = 1.60, 95%CI: 0.94–2.73, P = 0.080), with a marginal trend toward a longer OS in the HTI group. Patients in the HTI group obtained significantly prolonged median PFS (12.0 vs. 9.1 months; HR = 1.96, 95%CI:1.21–3.17; P = 0.005). No significant between-group differences were observed in ORR (58.7% vs. 43.5%; P = 0.144) or DCR (84.8% vs. 80.4%; P = 0.582). The incidences of grade 1–2 fever (8.7% vs. 28.3%; P < 0.001) and abdominal pain (6.5% vs. 32.6%; P < 0.001) were markedly lower in the HTI group. No treatment-related deaths were documented in either cohort.

Conclusions

HTI prolonged PFS and reduced mild local AEs compared with TTI, with similar OS, ORR and DCR. This regimen is promising for this high-risk population, and further prospective trials are needed for validation.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide. In China, approximately 64% of HCC patients are diagnosed at intermediate or advanced stages and thus cannot receive curative resection [1, 2]. or unresectable HCC (uHCC), combined regimens of conventional transarterial chemoembolization (TACE) and targeted immunotherapy (TI) have improved clinical outcomes [3, 4], while treatment efficacy varies greatly by tumor burden [5, 6].

For uHCC with high tumor burden, TACE monotherapy yields unsatisfactory results. Large tumor lesions often fail to achieve complete necrosis, and repeated TACE sessions may impair liver function [7, 8]. Early combination of TI with

TACE may improve tumor control in this subgroup [9]. Meanwhile, FOLFOX-based hepatic arterial infusion chemotherapy (HAIC) has become an important locoregional treatment. It delivers high-dose chemotherapy directly to tumor tissues and shows favorable efficacy in patients with large HCC, portal vein tumor thrombosis (PVTT) or extrahepatic metastasis [10–12].

Previous comparative studies have demonstrated that HAIC provides better tumor regression, higher conversion-to-resection rates, improved survival and fewer severe adverse events (AEs) than TACE, either as monotherapy or combined with systemic agents [13–15]. Furthermore, triplet regimens such as HAIC plus TI (HTI) and TACE plus TI (TTI) have shown better survival and tumor control than locoregional or systemic therapy alone[3, 11, 16–18]. However, direct evidence comparing HTI and TTI in this high-tumor-burden, highly aggressive cohort of BCLC stage C uHCC patients meeting the "up-to-11" criteria (sum of tumor number and maximum diameter > 11) remains limited.

Therefore, we conducted this multicenter retrospective cohort study using propensity score matching (PSM) to compare the efficacy and safety of HTI and TTI. Our findings aim to provide clinical evidence for individualized treatment selection in this high-risk population.

Methods

Study design and patients

This multicenter retrospective cohort study consecutively screened patients with uHCC and high tumor burden from six tertiary hospitals in China between January 2020 and June 2024 (Fig. 1).

Inclusion criteria were as follows: (1) Age ≥ 18 years; (2) HCC diagnosed by imaging criteria and/or histopathology; (3) Unresectable HCC confirmed by a multidisciplinary team; (4) Meeting the predefined Up-to-11 criterion (total tumor number plus maximum tumor diameter > 11) [9]; (5) BCLC stage C (with PVTT or extrahepatic metastasis); (6) ECOG performance status 0–1; (7) Child-Pugh class A-B liver function; (8) no prior HCC-related locoregional or systemic antitumor therapy; (9) at least one measurable lesion per the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Exclusion criteria were: (1) Receiving fewer than two cycles of triple combination therapy, to ensure adequate treatment exposure; (2) Receiving HAIC with raltitrexed plus oxaliplatin; (3) Dominant extrahepatic tumor blood supply confirmed by angiography, which contraindicated standard hepatic arterial infusion; (4) Receiving TACE with drug-eluting beads; (5) Combined with other malignant tumors; (6) Severe cardiopulmonary diseases, severe hepatic or renal dysfunction, or clinically significant coagulation disorders; (7) Missing key baseline data or follow-up information after treatment.

Treatment procedure

All patients received FOLFOX regimen for HAIC. Drugs were delivered via selective hepatic arterial catheterization following institutional standard protocols. Oxaliplatin (130 mg/m²) was infused over 2 hours, followed by leucovorin (400 mg/m²) over 2 hours, and fluorouracil (400 mg/m² bolus) plus fluorouracil (2400 mg/m² continuous infusion for 46 hours). Treatment was repeated every 3–4 weeks, for up to six cycles. Dose adjustment was performed based on patient tolerance and laboratory results at the physician’s discretion.

All TACE procedures were conventional TACE, using an iodized oil-chemotherapy emulsion followed by embolization with non-drug-loaded microspheres. Superselective catheterization of tumor-feeding arteries was performed whenever feasible to maximize tumor targeting and preserve liver function. Chemotherapeutic agents included epirubicin or pirarubicin (total dose ≤ 60 mg). Embolic materials included gelatin sponge particles and/or bland microspheres. Repeat TACE was performed per the Chinese clinical practice guidelines for TACE [19] if significant viable tumors were detected on follow-up imaging.

Targeted immunotherapy

TI regimens were selected based on medical insurance policies and patient willingness. The applied combinations included: atezolizumab (1200 mg intravenously every 3 weeks) plus bevacizumab (5 mg/kg intravenously every 3 weeks); sintilimab (200 mg intravenously every 3 weeks) plus bevacizumab (5 mg/kg intravenously every 3 weeks); camrelizumab (200 mg intravenously every 3 weeks) plus apatinib (250 mg orally once daily) and tislelizumab (200 mg intravenously every 3 weeks) plus donafenib (200 mg orally twice daily).

TI was initiated within 2 weeks after the first HAIC or TACE session. Dose reduction or temporary interruption was allowed for targeted agents in case of treatment-related AEs. Immunotherapy doses were not reduced, while treatment could be delayed or interrupted and resumed after symptom relief per standard guidelines.

Assessment and outcomes

Imaging re-evaluation was conducted every 4–8 weeks after the first treatment cycle. Two independent radiologists blinded to group allocation assessed the best overall tumor response; discrepancies were resolved by consensus discussion. The primary endpoint was overall survival (OS, time from first locoregional therapy to all-cause death or study cutoff). Secondary endpoints included progression-free survival (PFS, time from first locoregional therapy to radiologically confirmed progression, all-cause death, or cutoff), objective response rate (ORR, proportion of complete response [CR] + partial response [PR]), disease control rate (DCR, CR + PR + stable disease [SD]), and AEs. AEs were assessed using version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

HAIC was discontinued after six cycles in patients without disease progression (PD), or intolerable toxicity. TACE was repeated as needed based on imaging findings, and TI was maintained continuously. All patients were followed up regularly until death or the study cutoff date (June 30, 2025). Patient enrollment was closed on June 30, 2024, to ensure a minimum 12-month follow-up for survival analysis.

Propensity score matching analysis

To minimize selection bias and confounding, propensity scores were estimated using a binary logistic regression model. Covariates were prespecified based on clinical relevance and baseline imbalance and included cirrhosis, tumor number, PVTT status, and extrahepatic metastasis. Patients were matched 1:1 using nearest-neighbor matching with a caliper of 0.02 without replacement. Covariate balance after matching was assessed using standardized mean differences, with values < 0.1 indicating adequate balance. Analyses in the matched cohort were performed accounting for the matched-pair structure.

Statistical analysis

SPSS 26.0 (IBM Corporation, Somers, NY) and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for analyses. Continuous variables were expressed as mean ± SD (t-test) or median (IQR) (Mann-Whitney U test). Categorical variables were summarized as counts (percentages) (χ^2 test or Fisher's exact test). Survival outcomes were estimated by Kaplan-Meier method and compared by log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional hazards regression models. Univariate and multivariable Cox regression identified outcome-related factors (variables with $P < 0.1$ in univariate analysis entered multivariable model). All tests were two-sided ($P < 0.05$ for significance). Survival time was right censored at last follow-up for patients without endpoint events.

Results

Patient characteristics

A total of 175 eligible patients were enrolled, including 63 patients in the HTI group and 112 in the TTI group. After 1:1 PSM, 46 matched pairs were generated. Before PSM, the HTI group had higher proportions of patients with cirrhosis, PVTT and more than 3 tumors, while the TTI group had a higher rate of extrahepatic metastasis. Baseline characteristics were well balanced between the two groups after PSM (Table 1).

Table 1
Baseline characteristics pre-PSM and post-PSM.

Characteristics	Pre-PSM				Post-PSM			
	Total (n = 175)	HTI (n = 63)	TTI (n = 112)	P value	Total (n = 92)	HTI (n = 46)	TTI (n = 46)	P value
Age, n (%)				0.504				1.000
≤ 65 years	131 (74.9)	49 (77.8)	82 (73.2)		70 (76.1)	35 (76.1)	35 (76.1)	
> 65 years	44 (25.1)	14 (22.2)	30 (26.8)		22 (23.9)	11 (23.9)	11 (23.9)	
Sex, n (%)				0.536				0.246
Female	32 (18.3)	10 (15.9)	22 (19.6)		14 (15.2)	5 (10.9)	9 (19.6)	
Male	143 (81.7)	53 (84.1)	90 (80.4)		78 (84.8)	41 (89.1)	37 (80.4)	
HBV, n (%)	144 (82.3)	54 (85.7)	90 (80.4)	0.373	78 (84.8)	40 (87.0)	38 (82.6)	0.562
Cirrhosis, n (%)	104 (59.4)	46 (73.0)	58 (51.8)	0.006	64 (69.6)	31 (67.4)	33 (71.7)	0.650
ECOG, n (%)				0.553				0.833
0	92 (52.6)	35 (55.6)	57 (50.9)		53 (57.6)	27 (58.7)	26 (56.5)	
1	83 (47.4)	28 (44.4)	55 (49.1)		39 (42.4)	19 (41.3)	20 (43.5)	
Child-Pugh class, n (%)				0.517				0.492
A	130 (74.3)	45 (71.4)	85 (75.9)		65 (70.7)	31 (67.4)	34 (73.9)	
B	45 (25.7)	18 (28.6)	27 (24.1)		27 (29.4)	15 (32.6)	12 (26.1)	
Tumor diameter (cm), n (%)				0.140				0.834
< 10	88 (50.3)	27 (42.9)	61 (54.5)		49 (53.3)	24 (52.2)	25 (54.4)	
≥ 10	87 (49.7)	36 (57.1)	51 (45.5)		43 (46.7)	22 (47.8)	21 (45.7)	
Tumor number, n (%)				0.011				0.804
≤ 3	54 (30.9)	12 (19.1)	42 (37.5)		21 (22.8)	10 (21.7)	11 (23.9)	
> 3	121 (69.1)	51 (81.0)	70 (62.5)		71 (77.2)	36 (78.3)	35 (76.1)	

Characteristics	Pre-PSM				Post-PSM			
	Total (n = 175)	HTI (n = 63)	TTI (n = 112)	P value	Total (n = 92)	HTI (n = 46)	TTI (n = 46)	P value
Tumor distribution, n (%)				0.238				0.270
Uni-lobar	77 (44.0)	24 (38.1)	53 (47.3)		31 (33.7)	13 (28.3)	18 (39.1)	
Bi-lobar	98 (56.0)	39 (61.9)	59 (52.7)		61 (66.3)	33 (71.7)	28 (60.9)	
AFP (ng/mL)				0.078				0.529
< 400	96 (54.9)	29 (46.0)	67 (59.8)		51 (55.4)	27 (58.7)	24 (52.2)	
≥ 400	79 (45.1)	34 (54.0)	45 (40.2)		41 (44.6)	19 (41.3)	22 (47.8)	
PVTT, n (%)				< .001				0.599
Absence	65 (37.1)	9 (14.3)	56 (50.0)		18 (19.6)	8 (17.4)	10 (21.7)	
Presence	110 (62.9)	54 (85.7)	56 (50.0)		74 (80.4)	38 (82.6)	36 (78.3)	
Extrahepatic Metastases, n (%)				< .001				0.656
Absence	99 (56.6)	46 (73.0)	53 (47.3)		62 (67.4)	32 (69.6)	30 (65.2)	
Presence	76 (43.4)	17 (27.0)	59 (52.7)		30 (32.6)	14 (30.4)	16 (34.8)	

Data are expressed as n (%) or quartile. Abbreviations: PSM, propensity score matching; HTI, hepatic artery infusion chemotherapy plus targeted immunotherapy; TTI, transarterial chemoembolization plus targeted immunotherapy; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis.

In the matched cohort, 84.8% of patients were male, and 84.8% had hepatitis B virus (HBV) infection. The maximum tumor diameter was greater than 10 cm in 46.7% of patients, and 32.6% had extrahepatic metastasis. PVTT was detected in 80.4% of patients, with VP1, VP2, VP3 and VP4 subtypes accounting for 1.1%, 7.6%, 36.9% and 34.8%, respectively.

After PSM, the HTI group had a median of 4.0 HAIC sessions (IQR, 3.0–4.0) and a median TI duration of 11.0 months (IQR, 6.3–17.8). The TTI group had a median of 4.0 TACE sessions (IQR, 2.0–6.0) (P = 0.391) and a median TI duration of 9.8 months (IQR, 5.5–12.2) (P = 0.232).

Survival outcomes

Before PSM, the median follow-up was 15.0 months (IQR, 8.6–25.0). A total of 34 patients (54.0%) in the HTI group and 64 patients (57.1%) in the TTI group died. The HTI group had similar median OS (21.0 vs. 18.0 months; HR = 1.27, 95% CI 0.83–1.92, P = 0.267) but longer median PFS (12.0 vs. 10.9 months; HR = 1.60, 95% CI 1.11–2.32, P = 0.011) versus the TTI group (Fig. 2A-B).

After PSM, the median follow-up remained 15.0 months (IQR, 9.0–23.6). Twenty-five patients (54.3%) in the HTI group and 31 patients (67.4%) in the TTI group died. Median OS showed a marginal statistical difference between groups (18.0 vs 16.3 months; HR = 1.60, 95% CI: 0.94–2.73, P = 0.080). The HTI group still had a significantly longer median PFS (12.0 vs 9.1 months; HR = 1.96, 95% CI: 1.21–3.17, P = 0.005) (Fig. 2C-D).

Tumor response

Before PSM, the HTI group achieved better overall tumor response (P < 0.001), which was mainly attributed to a higher CR rate (19.1% vs 1.8%) (Table 2). Two patients in the HTI group received conversion resection.

Table 2
Best tumor response pre-PSM and post-PSM.

	pre-PSM			post-PSM		
	HTI (n = 63)	**TTI (n = 112)**	**P**	**HTI (n = 46)**	**TTI (n = 46)**	**P**
Best response			< .001			0.159
CR	12 (19.0)	2 (1.8)		7 (15.2)	1 (2.2)	
PR	24 (38.1)	59 (52.7)		19 (41.3)	19 (41.3)	
SD	14 (22.2)	30 (26.8)		13 (28.3)	17 (37.0)	
PD	13 (20.6)	21 (18.8)		7 (15.2)	9 (19.6)	
ORR	37 (58.7)	61 (54.5)	0.585	27 (58.7)	20 (43.5)	0.144
DCR	50 (79.4)	91 (81.3)	0.762	39 (84.8)	37 (80.4)	0.582

Data are expressed as n (%) or quartile. Abbreviations: PSM, propensity score matching; HTI, hepatic artery infusion chemotherapy plus targeted immunotherapy; TTI, transarterial chemoembolization plus targeted immunotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

After PSM, the overall objective tumor response was similar between the two groups. No significant differences were found in overall treatment response (P = 0.159), ORR (58.7% vs 43.5%, P = 0.144) or DCR (84.8% vs 80.4%, P = 0.582). The rates of CR, PR, SD and PD were 15.2%, 41.3%, 28.3% and 15.2% in the HTI group, versus 2.2%, 41.3%, 37.0% and 19.6% in the TTI group.

Univariate and multivariate analysis

A multivariate Cox proportional hazards regression model was employed to identify the prognostic factors for OS and PFS. Post-PSM, ECOG (1 vs. 0; HR = 2.06, 95% CI 1.15–3.93, P = 0.016), tumor diameter (≥ 10 vs. <10 cm; HR = 1.95, 95% CI 1.11–3.40, P = 0.020), and sex (male vs. female; HR = 0.38, 95% CI 0.19–0.73, P = 0.004) were significantly associated with OS. Treatment (TTI vs. HTI; HR = 1.87, 95% CI 1.15–3.02, P = 0.011) and sex (male vs. female; HR = 0.35, 95% CI 0.19–0.67, P = 0.001) were correlated with PFS (Table 3). The results before PSM are presented in Supplementary Table 1.

Table 3
Univariate and multivariate analyses of predictors of OS and PFS post-PSM.

Characteristics	OS				PFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Treatment (TTI vs. HTI)	1.60 (0.94–2.72)	0.084			1.96 (1.21–3.17)	0.006	1.87 (1.15–3.02)	0.011
Age (years) (> 65 vs. ≤ 65)	1.47 (0.81–2.67)	0.205			0.92 (0.52–1.62)	0.763		
Sex (Male vs. Female)	0.38 (0.20–0.71)	0.003	0.38 (0.19–0.73)	0.004	0.31 (0.17–0.58)	< .001	0.35 (0.19–0.67)	0.001
HBV (Presence vs. Absence)	0.98 (0.44–2.17)	0.952			1.14 (0.58–2.23)	0.709		
Cirrhosis (Presence vs. Absence)	1.16 (0.65–2.08)	0.611			1.06 (0.63–1.79)	0.814		
ECOG score (1 vs. 0)	1.88 (1.11–3.20)	0.019	2.06 (1.12–3.78)	0.019	1.65 (1.02–2.65)	0.040		
Child-Pugh class (B vs. A)	2.00 (1.15–3.47)	0.014			1.90 (1.15–3.14)	0.012		
Tumor diameter (cm) (≥ 10 vs. < 10)	1.70 (1.01–2.88)	0.049	1.95 (1.11–3.40)	0.020	1.43 (0.89–2.29)	0.138		
Tumor number (≥ 3 vs. < 3)	1.04 (0.53–2.02)	0.914			0.89 (0.51–1.55)	0.670		
Tumor distribution (Bi-lobar vs. Uni-lobar)	1.07 (0.61–1.90)	0.812			0.92 (0.56–1.51)	0.737		
AFP (μg/L) (≥ 400 vs. < 400)	1.45 (0.85–2.46)	0.173			1.13 (0.70–1.82)	0.613		
PVTT (Presence vs. Absence)	1.00 (0.51–1.99)	0.992			0.84 (0.46–1.55)	0.576		
Extrahepatic Metastases (Presence vs. Absence)	0.67 (0.37–1.22)	0.195			1.17 (0.71–1.90)	0.539		

Abbreviations: OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; HTI, hepatic artery infusion chemotherapy plus targeted immunotherapy; TTI, transarterial chemoembolization plus targeted immunotherapy; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVTT, Portal vein tumor thrombosis.

Adverse events and safety

No significant differences were observed in the overall incidence of AEs, grade 1–2 AEs, or grade 3–4 AEs between the two groups before and after PSM. Pre-PSM (Supplementary Table 2), compared with the TTI group, the HTI group had lower rates of grade 1–2 fever (9.5% vs. 40.2%, $P < 0.001$), abdominal pain (8.0% vs. 33.0%, $P < 0.001$), and grade 3–4 elevated ALT (0 vs. 9.8%, $P = 0.025$) and AST (1.6% vs. 11.6%, $P = 0.019$). Post-PSM (Table 4), the HTI group remained with lower grade 1–2 fever (8.7% vs. 28.3%, $P < 0.001$) and abdominal pain (6.5% vs. 32.6%, $P < 0.001$).

Table 4
Treatment related adverse events post-PSM.

Adverse event	Any grade			Grade 1/2			Grade 3/4		
	HTI (n = 46)	TTI (n = 46)	P	HTI (n = 46)	TTI (n = 46)	P	HTI (n = 46)	TTI (n = 46)	P
Any adverse events	24 (52.2)	27 (58.7)	0.529	23 (50.0)	27 (58.7)	0.402	10 (21.7)	13 (28.3)	0.470
Elevated ALT	5 (10.9)	6 (13.0)	0.748	5 (10.9)	3 (6.5)	0.711	0 (0)	3 (6.5)	0.240
Elevated AST	5 (10.9)	9 (19.6)	0.246	4 (8.7)	2 (4.4)	0.673	1 (2.2)	7 (15.2)	0.064
Hyperbilirubinemia	4 (8.7)	7 (15.2)	0.335	2 (4.4)	5 (10.9)	0.432	2 (4.4)	2 (4.4)	1.000
Hepatic encephalopathy	0 (0)	1 (2.2)	1.000	0 (0)	1 (2.2)	1.000			
Fatigue	7 (15.2)	10 (21.7)	0.420	7 (15.2)	10 (21.7)	0.420			
Fever	4 (8.7)	13 (28.3)	0.016	4 (8.7)	13 (28.3)	0.016			
Nausea	9 (19.6)	5 (10.9)	0.246	9 (19.6)	5 (10.9)	0.246			
Vomiting	8 (17.4)	6 (13.0)	0.562	7 (15.2)	6 (13.0)	0.765	1 (2.2)	0 (0)	1.000
Abdominal pain	4 (8.7)	15 (32.6)	0.005	3 (6.5)	15 (32.6)	0.002	1 (2.2)	0 (0)	1.000
Diarrhea	0 (0)	2 (4.4)	0.475	0 (0)	1 (2.17)	1.000	0 (0)	1 (2.17)	1.000
Constipation	0 (0)	1 (2.2)	1.000	0 (0)	1 (2.17)	1.000			
Leukopenia	2 (4.4)	2 (4.4)	1.000	0 (0)	2 (4.4)	0.475	2 (4.4)	0 (0)	0.475
Neutropenia	1 (2.2)	0 (0)	1.000				1 (2.17)	0 (0)	1.000
Lymphopenia	0 (0)	2 (4.4)	0.475	0 (0)	1 (2.17)	1.000	0 (0)	1 (2.2)	1.000
Thrombocytopenia	5 (10.9)	6 (13.0)	0.748	3 (6.5)	4 (8.7)	1.000	2 (4.4)	2 (4.4)	1.000
Proteinuria	1 (2.2)	2 (4.4)	1.000	1 (2.2	2 (4.4)	1.000			
Hypertension	2 (4.4)	3 (6.5)	1.000	2 (4.4)	3 (6.5)	1.000			
Hand-foot skin reaction	2 (4.4)	3 (6.5)	1.000	2 (4.4)	3 (6.5)	1.000			

Adverse event	Any grade			Grade 1/2			Grade 3/4		
	HTI (n = 46)	TTI (n = 46)	P	HTI (n = 46)	TTI (n = 46)	P	HTI (n = 46)	TTI (n = 46)	P
Gingival bleeding	0 (0)	1 (2.2)	1.000	0 (0)	1 (2.2)	1.000			
EGVB	3 (6.5)	1 (2.2)	0.609	2 (4.4)	0 (0)	0.475	2 (4.4)	1 (2.2)	1.000
Dental ulcer	0 (0)	1 (2.2)	1.000	0 (0)	1 (2.2)	1.000			
RCCEP	3 (6.5)	0 (0)	0.240	3 (6.5)	0 (0)	0.240			
Hypothyroidism	2 (4.4)	3 (6.5)	1.000	2 (4.4)	3 (6.5)	1.000			
Gastrointestinal perforation	1 (2.2)	0 (0)	1.000	1 (2.2)	0 (0)	1.000			
Immune-related dermatitis	0 (0)	2 (4.4)	0.475	0 (0)	1 (2.2)	1.000	0 (0)	1 (2.2)	1.000
Immune-related myocarditis	1 (2.2)	0 (0)	1.000	1 (2.2)	0 (0)	1.000			

Data are expressed as n (%). Abbreviations: PSM, propensity score matching; HTI, hepatic artery infusion chemotherapy plus targeted and immunotherapy; TTI, transarterial chemoembolization plus targeted and immunotherapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGVB, esophageal and gastric variceal bleeding; RCCEP, reactive cutaneous capillary endothelial proliferation.

Post-PSM, common AEs in the HTI group were nausea (19.6%), vomiting (17.4%), fatigue (15.2%), thrombocytopenia (10.9%), elevated ALT (10.9%), and elevated AST (10.9%). In the TTI group, common AEs were abdominal pain (32.6%), fever (28.3%), fatigue (21.7%), elevated AST (19.6%), hyperbilirubinemia (15.2%), thrombocytopenia (13.0%), vomiting (13.0%), and elevated ALT (13.0%). All AEs were manageable with symptomatic/supportive care; no treatment-related deaths occurred.

Discussion

Using PSM to balance baseline characteristics, this multicenter retrospective study compared the clinical outcomes of HTI and TTI in BCLC stage C uHCC patients meeting the Up-to-11 criterion with high tumor burden. In the matched cohort, the HTI regimen significantly prolonged PFS and reduced mild adverse events related to interventional therapy. No significant differences were found in median OS, ORR or DCR between the two groups. These findings indicate that HTI can effectively delay tumor progression in this aggressive high tumor burden population, while its potential survival benefit requires further verification.

High tumor burden is a key but controversial prognostic factor in uHCC research. Our enrolled patients met the Up-to-11 criterion [7, 9] and were complicated with PVTT or extrahepatic metastasis, covering multiple adverse prognostic factors including large tumor size, numerous lesions, major vascular invasion and distant metastasis [20]. Recent studies on triple combination regimens for uHCC (e.g., FOLFOX-HAIC + TI or c-TACE + TI) reported median

OS of 18.7–27.2 months, median PFS of 6.6–15.4 months and ORR of 47.3%-88.6% [3, 11, 16–18, 21]. However, studies focusing specifically on uHCC with high tumor burden remain scarce. One similar study focusing on this population adopted combined TACE and HAIC plus immunotherapy, with an ORR of 62.2% and median PFS of 10.1 months [9]. Its PFS result was between the values of our two groups, with a slightly higher ORR. Although cross-study comparison has limitations, our patients had heavier tumor burden and worse baseline status, including higher rates of cirrhosis, Child-Pugh B liver function and ECOG 1 performance status. In addition, the clinical value of dual locoregional therapy (TACE plus HAIC) is still under debate [22].

The PFS superiority of HTI is closely related to the pharmacological and biological characteristics of HAIC. Regional high-dose chemotherapy exerts strong tumor debulking effects and induces immunogenic cell death, which releases tumor-associated antigens and damage-related molecular patterns to activate anti-tumor immune responses [23, 24]. Combined anti-angiogenic therapy normalizes tumor vasculature, improves blood perfusion and reduces immunosuppressive cell infiltration, thereby enhancing the efficacy of immune checkpoint inhibitors [25]. The triple regimen combining tumor reduction, tumor microenvironment remodeling and immune activation produces synergistic anti-tumor effects for large and highly immunosuppressive HCC. The lack of significant OS benefit despite prolonged PFS suggests that HAIC-based triple therapy mainly improves local tumor control and delays progression. Long-term survival is affected by subsequent treatment strategies, liver reserve function, management of extrahepatic lesions, as well as sample size and follow-up duration in this study.

After PSM, ECOG performance status and tumor diameter ≥ 10 cm were independent risk factors for poor OS. These results are consistent with previous reports [7, 11, 14, 20, 26], confirming that physical status and tumor burden are core determinants of clinical outcomes. Treatment regimen was also an independent prognostic factor: TTI was associated with higher progression risk than HTI, which further proved the better tumor control ability of HTI. Additionally, male patients tended to have longer OS and PFS than females, which has also been reported in HCC patients receiving atezolizumab plus bevacizumab [27]. Since the correlation between sex and prognosis remains inconsistent across studies, sex-stratified subgroup analyses are needed in future research.

Consistent with previous reports, our study confirmed the favorable safety profile of HTI. It is associated with better short-term liver function and higher continuity of subsequent systemic treatment [28–30]. Before PSM, the HTI group had fewer cases of grade 3–4 ALT/AST elevation. Both before and after PSM, the incidence of grade 1–2 fever and abdominal pain was obviously lower in the HTI group. Distinct toxicity characteristics were observed between the two regimens: HAIC-based therapy mainly causes chemotherapy-related gastrointestinal reactions and myelosuppression, while TACE is more likely to induce post-embolization syndrome including fever, abdominal pain and elevated bilirubin [3, 11, 14, 17, 31, 32]. Overall, most AEs were mild to moderate and could be controlled by dose adjustment, treatment interruption or supportive care.

Several limitations of this study should be acknowledged. First, residual confounding factors and selection bias cannot be completely eliminated even after PSM due to the retrospective design. Second, the included TI regimens were heterogeneous in real-world clinical practice, and the limited sample size failed to conduct subgroup analyses for different combinations, which may mask potential interactions between systemic drugs and locoregional therapy. Third, our prognostic models only adopted routine clinical indicators, lacking molecular biomarkers for refined risk stratification and biological mechanism exploration. Finally, most enrolled patients had HBV-related HCC combined with cirrhosis, which may reduce the generalizability of our conclusions to other etiological HCC populations.

Conclusion

For BCLC stage C uHCC patients meeting the Up-to-11 high tumor burden criterion, FOLFOX-HAIC combined with targeted immunotherapy achieved longer median PFS and fewer mild locoregional adverse events compared with conventional TACE plus targeted immunotherapy, without increasing the risk of severe AEs. Median OS, ORR and DCR were comparable between the two groups. This study provides real-world evidence for individualized selection of locoregional therapy in targeted immunotherapy-based combination regimens, according to tumor burden and patient risk profiles.

Abbreviations

HAIC
Hepatic Arterial Infusion Chemotherapy
TI
Targeted Immunotherapy
TACE
Transarterial Chemoembolization
HCC
Hepatocellular Carcinoma
uHCC
Unresectable Hepatocellular Carcinoma
BCLC
Barcelona Clinic Liver Cancer
PSM
Propensity Score Matching
OS
Overall Survival
PFS
Progression-Free Survival
ORR
Objective Response Rate
DCR
Disease Control Rate
AEs
Adverse Events
CR
Complete Response
PR
Partial Response
SD
Stable Disease
PD
Disease Progression
PVTT
Portal Vein Tumor Thrombosis

ECOG
Eastern Cooperative Oncology Group
mRECIST
modified Response Evaluation Criteria in Solid Tumors
CTCAE
Common Terminology Criteria for Adverse Events
ALT
Alanine Aminotransferase
AST
Aspartate Aminotransferase
HR
Hazard Ratio
CI
Confidence Interval
IQR
Interquartile Range
TKIs
Tyrosine Kinase Inhibitors
ICIs
Immune Checkpoint Inhibitors

Declarations

Data availability

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

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Wuxi People's Hospital, Nanjing Medical University (approval no. KY23101) and conducted in accordance with the Declaration of Helsinki. Given the retrospective nature of the study, the Ethics Committee granted an exemption for written informed consent.

Authors contributions

Hao-Huan Tang: investigation; data curation; methodology; formal analysis; writing-original draft; writing-review & editing. Qi Jiang: investigation; data curation; methodology; formal analysis; writing-original draft. Ming-Qing Zhang: data curation; methodology; writing-original draft. Zi-Chen Zhang: data curation; investigation; formal analysis; supervision; validation. Chen Fan: data curation; investigation; formal analysis; supervision; validation. Wei-Dong Wang: data curation; investigation; formal analysis; supervision; validation. Shu-Shu Li: data curation; software; formal analysis. Jia-Xi Liu: data curation; software; formal analysis. Hai-Bo Shao: investigation; methodology; revision; writing-review & editing. Lin-Feng Zhou: investigation; methodology; revision; resources; writing-review & editing. Xiao-Li Zhu: investigation; methodology; revision; resources; writing-review & editing.

Financial support

None.

Consent for publication

All authors agreed to the submission and publication of this study to this journal.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgments

None

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Figures

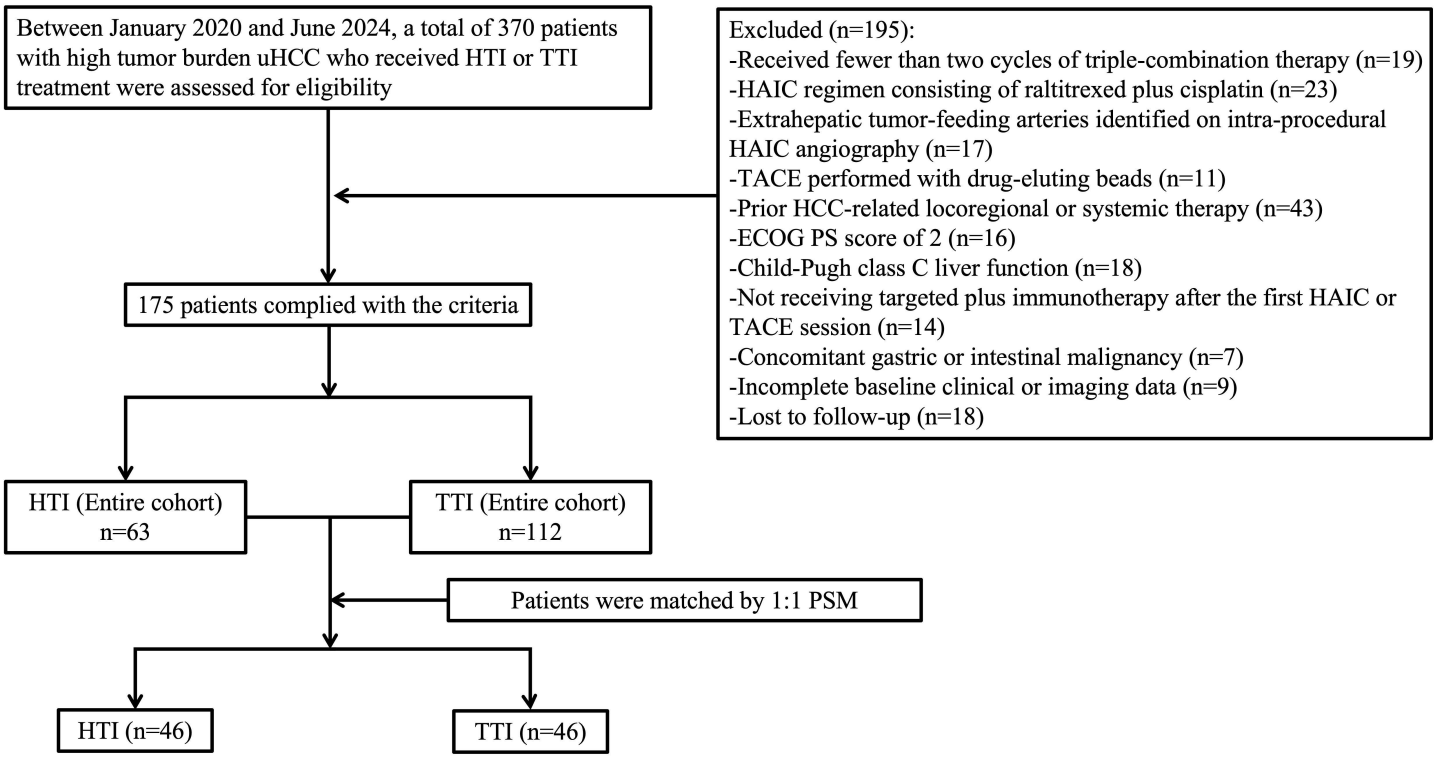


Figure 1

Flowchart of the patient selection.

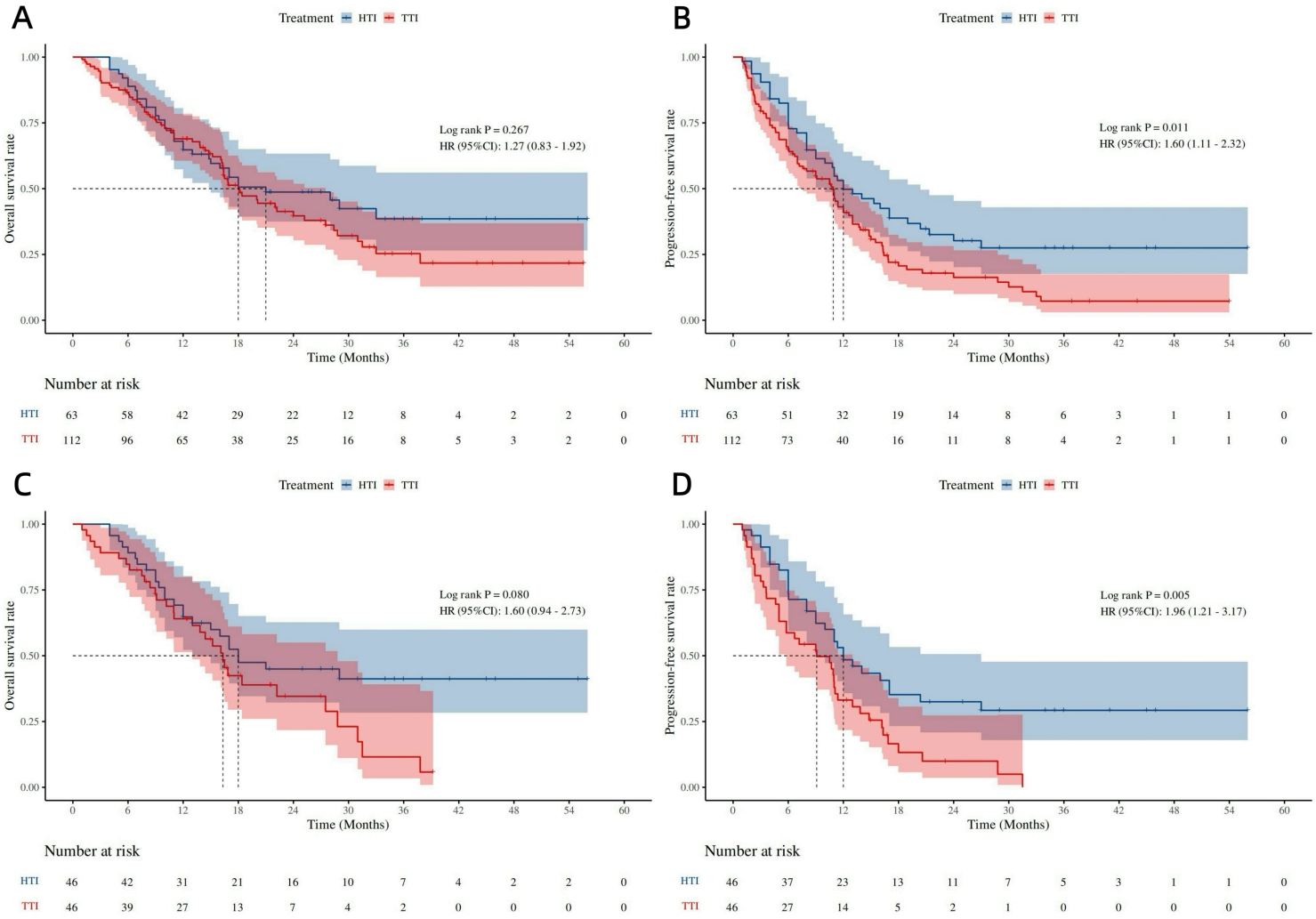


Figure 2

Kaplan-Meier curves for OS and PFS in patients receiving HTI or TTI before (A-B) and after (C-D) PSM. P values were calculated using the log-rank test. OS: overall survival; PFS: progression-free survival; HTI: hepatic artery infusion chemotherapy plus targeted immunotherapy; TTI: transarterial chemoembolization plus targeted immunotherapy; PSM: propensity score matching; HR: hazard ratio; CI: confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx