Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and Safety of the Multi-Level Comprehensive Collateral Artery Embolism Sequential Hepatic Arterial Infusion Chemotherapy, Combined with TKI and ICI, for Unresectable Huge Hepatocellular Carcinoma (>10cm): A Propensity Score Matching Cohort Study

Hao-yang Tan[1,*], Shuang-quan Liu[1,*], Yan-han Liu[2,*], Jiu-ling Zheng[1], Hua-guo Feng[1]

[1]Department of Hepatobiliary Surgery, The Chongqing University Jiangjin Hospital, School of Medicine, Chongqing University, Chongqing, People's Republic of China; [2]Department of Radiology, The Chongqing University Jiangjin Hospital, School of Medicine, Chongqing University, Chongqing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hua-guo Feng; Jiu-ling Zheng, Department of Hepatobiliary Surgery, The Chongqing University Jiangjin Hospital, School of Medicine, Chongqing University, Chongqing, People's Republic of China, Email fenghuaguo@126.com; 740605764@qq.com

Objective: This retrospective study was conducted to evaluate the effectiveness and safety of a new combination therapy of the multi-level comprehensive collateral artery embolism (CAE) sequential hepatic arterial infusion chemotherapy (HAIC), tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI) for unresectable huge hepatocellular carcinoma (>10cm) patients.

Methods: A propensity score-matching (PSM) cohort study was conducted. The initial tumor response, treatment-related adverse events, and survival outcomes were compared. The Forestplot package was used to visualize and interpret forest plots of overall survival subgroup analyses. Univariate and multivariate analyses were conducted to explore the risk factors of overall survival.

Results: Thirty-one pairs of patients were evaluated after PSM. There were statistically significant differences in the initial tumor response and objective response rate (ORR) between the two groups (74.2% vs 48.4%, P=0.037). Compared with the "HAIC" group, the incidence of abdominal pain was higher in the "CAE+HAIC" group (71.0% vs 41.9%, P=0.021). The OS and progression-free survival (PFS) of the "CAE+HAIC" group were longer than those of the "HAIC" group (OS: HR=0.439, 95% CI: 0.199–0.970, P=0.042; PFS: HR=0.475; 95% CI: 0.252–0.895; P=0.021). The CAE (HR=0.403, 95% CI: 0.213–0.762; P=0.005), prealbumin levels <170 mg/L (HR=2.195, 95% CI: 1.226–3.929; P=0.008), and lactic dehydrogenase levels >245 U/L (HR=2.136, 95% CI: 1.215–3.757; P=0.008) were independent risk factors of OS.

Conclusions: The multi-level comprehensive CAE sequential HAIC, combined with TKI and ICI, can improve tumor response and prolong survival time in unresectable huge HCC patients while remaining safe and tolerable.

Keywords: hepatocellular carcinoma, collateral artery embolism, hepatic artery infusion chemotherapy, propensity score matching

Introduction

Hepatocellular carcinoma (HCC), widely recognized as the sixth most common cancer globally, is the third most common cause of cancer-related deaths, while it holds the fourth-highest incidence and the second-leading mortality rate in China.[1,2] Unfortunately, over 50% of patients were diagnosed with unresectable liver cancer, with a 5-year

Received: 12 June 2025
Accepted: 8 August 2025
Published: 19 August 2025

survival rate of less than 3%.[3] The first-line treatment for early-stage HCC is surgical resection, liver transplantation, or local ablation, whereas the main treatments for advanced HCC involve hepatic artery interventional therapy, radiotherapy, tyrosine kinase inhibitors (TKI), immune checkpoint inhibitors (ICI), traditional Chinese medicine,[4] and various combination therapies.[5] While international guidelines recommend ICI-based regimens, such as Atezolizumab plus bevacizumab or Tremelimumab plus durvalumab, as the first-line treatment for unresectable large HCC,[6,7] more aggressive approaches have shown promise in improving outcomes. A recent study shows that an integrated radiomic immunoscore model improves prognosis prediction and may guide HCC immunotherapy.[8] Transcatheter arterial chemoembolization (TACE), recommended as the first-line treatment for advanced HCC, can improve survival time and quality of life for unresectable HCC. However, for large unresectable HCC, it often requires multiple TACE or repeated TACE, which may impair liver function and stimulate tumor angiogenesis, hence promoting tumor growth and metastasis.[9]

Hepatic arterial infusion chemotherapy (HAIC) slowly delivers chemotherapy drugs directly into liver tumors through a catheter, enhancing localized anticancer drug concentration while minimizing systemic side effects.[10] A meta-analysis revealed that HAIC combined with TKI and ICI demonstrates promising therapeutic efficacy and favorable safety for unresectable advanced HCC.[11] This systematic review also found that the objective response rate (ORR) of the included studies ranged from 43.6% to 88.6%, with significant heterogeneity among studies. The reason is that some studies conducted only HAIC treatment, while others performed TACE+HAIC treatment. A recent study showed that TACE or transarterial embolization combined with HAIC has a manageable safety profile with improved survival benefits for unresectable HCC.[12] With the proposal of the precision cancer treatment concept, injury control intervention therapy deserves more attention.[13] During cancer treatment, it is essential not only to ensure efficacy but also to manage damage and prevent additional adverse reactions. In cases of unresectable huge HCC, with a diameter exceeding 10 cm, TACE +HAIC or HAIC administered independently may not adequately balance therapeutic efficacy with the associated risks of damage. A recent study revealed that TACE plus HAIC can significantly improve the overall response rate (ORR), time to progression, and overall survival (OS) with an acceptable safety profile for large HCC with major portal vein tumor thrombosis.[14] To ensure compatibility between therapeutic efficacy and the risk of damage, we are exploring new treatment avenues through the embolization of tumor collateral arteries. Most tumor arterial embolizations target the main blood vessels supplying the tumor; however, HAIC recommends focusing on embolizing tumor collateral arteries.[10] The extent and degree of collateral artery embolization remain unclear. To optimize treatment, we have enhanced the multi-level comprehensive collateral artery embolization (CAE) based on the Three-Stage Mixed Chemoembolic Regimen TACE.[15] We did not perform ultra-peripheral embolization with iodinated oil emulsion on the tumor; instead, we used sequential HAIC to minimize adverse reactions related to interventional embolization.

Therefore, this retrospective propensity score matching (PSM) cohort study was conducted to investigate the effectiveness and safety of multi-level comprehensive CAE sequential HAIC, combined with TKI and ICI, for unresectable huge HCC patients.

Materials and Methods

Patients

This retrospective analysis encompassed patients with unresectable huge HCC who received HAIC combined with TKI and ICI at the Hepatobiliary Surgery Department from January 2021 to October 2024. Eligible patients were categorized into the "CAE+HAIC" group and the "HAIC" group depending on their acceptance of collateral artery embolization. This study followed the guidelines of the Declaration of Helsinki and received approval from the Institutional Review Board of Chongqing University Jiangjin Hospital (KY20250528-003).

The inclusion criteria were delineated as follows: (1) Participants must be over 18 years of age; (2) Participants who had been pathologically or clinically diagnosed with HCC; (3) Availability of complete clinical data and medical history; (4) The tumor's maximum diameter exceeded 10 cm, and a multidisciplinary consultation prior to treatment confirmed that the hepatocellular carcinoma was unresectable; (5) All patients, along with their families, provided informed consent prior to treatment to authorize the retrospective review and documentation of medical records.

The exclusion criteria were as follows: (1) distant metastasis, such as those in the brain or lungs; (2) complicated with severe immune system, heart, lung, or kidney diseases; (3) incomplete medical information.

CAE+HAIC Procedures

The patients in the "CAE+HAIC" group underwent multi-level comprehensive collateral artery embolization and selective catheterization of the tumor-feeding artery. The Seldinger technique was utilized to routinely puncture the femoral artery, whereby a 5Fr sheath tube and catheter were sequentially introduced following successful puncture. Traditional selective catheterization is conducted on the abdominal trunk artery and the superior mesenteric artery for the purpose of angiography. This procedure aims to assess the blood supply to the lesion and identify any collateral circulation arteries (Figure 1A). A microcatheter was inserted superselectively into the collateral circulation arteries (Figure 1B). Initially, small particle size microspheres serve as the primary embolization material for distal peripheral collateral artery embolization, succeeded by the application of larger particle size embolization for proximal collateral arteries, thereby achieving multi-level comprehensive collateral artery embolization (Figure 1C). Subsequently, proceed to selectively insert the microcatheter into the arterial supply of the tumor. It is essential that the tip of the catheter adequately encompasses the entire vascular supply area of the tumor. Following this, confirm the satisfactory positioning of the catheter through angiography (Figure 1D). Stabilize the catheter's position by securing it around the femoral artery sheath and affixing it externally using 3M film. Additionally, the catheter should be sealed with heparin saline to mitigate the risk of thrombus formation. The catheter and sheath were removed after finishing the artery infusion chemotherapy. The patients in the "HAIC" group only underwent selective catheterization of the tumor-feeding artery and the infusion of chemotherapy drugs, without collateral artery embolization.

The modified FOLFOX-HAIC regimen was as follows: oxaliplatin 85mg/m^2 from hours 0–3 on day 1, leucovorin 400 mg/m^2 from hours 3–5, 5-fluorouracil 400 mg/m^2 injected at hour 5, and 5-fluorouracil 2500 mg/m^2 continuously

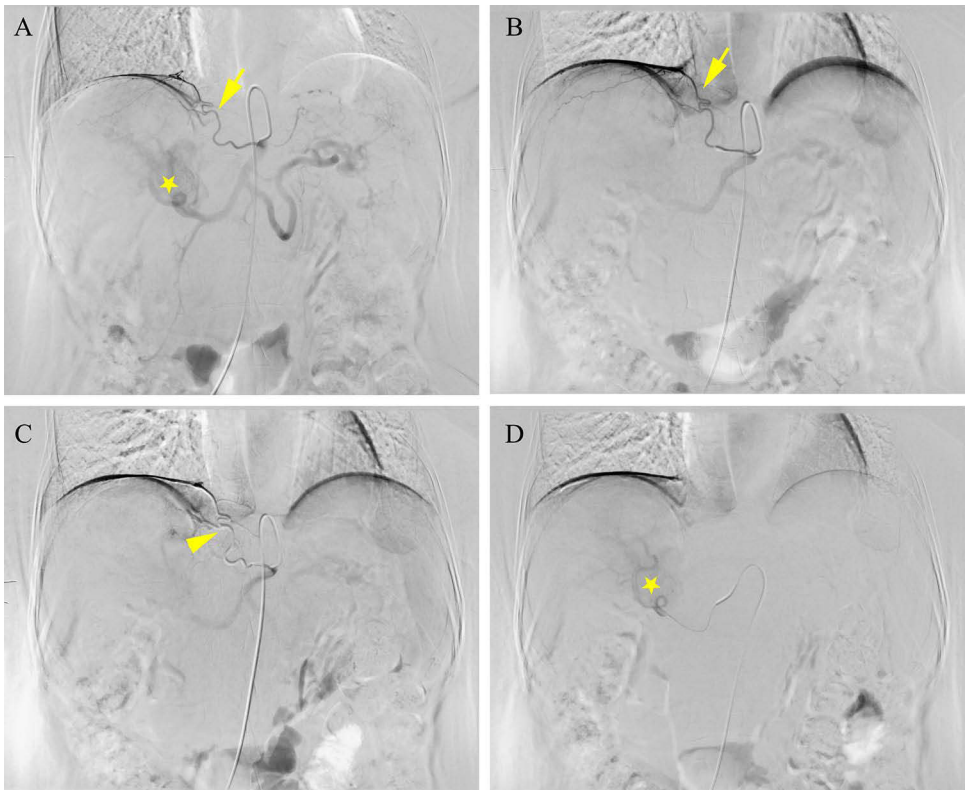

Figure 1 Main procedures of collateral artery embolism (CAE) combined with hepatic artery infusion chemotherapy (HAIC). (**A**) Hepatic artery angiography showed the main and collateral arteries of the tumor; (**B**) Super selection to tumor collateral artery angiography and stratified embolization; (**C**) Complete disappearance of tumor collateral arteries after stratified embolization; (**D**) Retain the microcatheter to the main artery of the tumor for HAIC. **Yellow long arrow**, the collateral artery of the tumor; **Yellow short arrow**, the collateral artery of the tumor after embolization; **Yellow star**, the main artery of the tumor.

https://doi.org/10.2147/JHC.S546588

pumped over 46 hours. The RALOX-HAIC regimen included: oxaliplatin 100mg/m^2 from hours 0–3 on day 1 and raltitrexed 3 mg/m^2 from hours 3–6 on day 1. HAIC therapy was administered every 3 weeks.

Comprehensive Systemic Therapy

In this study, every patient received first-line systemic therapy consisting of camrelizumab combined with apatinib or lenvatinib paired with tislelizumab. TKIs were administered daily at fixed doses of 8 mg for lenvatinib or 250 mg for apatinib. Tislelizumab was given at a dosage of 200 mg, with camrelizumab also prescribed at 200 mg. ICIs were administered intravenously once every three weeks. If significant side effects (grade > 3) arise during treatment, TKI and ICI dosages may need to be reduced or stopped.

Data Collection and Definition

Data for the entire group was gathered from an electronic medical record system. Each patient underwent regular follow-ups, either through outpatient visits or phone calls, scheduled monthly after treatment. Follow-ups needed to be completed by March 31, 2025.

The initial tumor response after six weeks of treatment was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[16] The objective response rate (ORR) represents the percentage of patients achieving either a complete response or a partial response under the mRECIST guidelines. The disease control rate (DCR) indicates the percentage of patients with a complete response, partial response, or stable disease. Tumor thrombus response was defined as no enhancement in the tumor thrombus or a reduction of at least 30% in the enhanced tumor thrombus area during the arterial enhancement phase. Progression-free survival (PFS) refers to the period from the commencement of HAIC to either tumor progression or death from any cause. Overall survival (OS) is calculated from the time of initial diagnosis until death due to any reason. Treatment-related adverse events were categorized according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 5.0).[17]

Propensity Score Matching

Logistic regression analysis was used to calculate propensity scores for all patients, considering baseline characteristics such as gender, age, body mass index (BMI), tumor size, performance status (PS), Child-Pugh class, and Albumin-bilirubin score (ALBI). The matching technique applied was the one-to-one nearest-neighbor approach with a caliper of 0.2 and no replacement. To assess the matching effect, variations in standardized deviation, the standard value range, and the kernel density map were analyzed.

Statistical Analysis

Statistical analysis was performed using STATA/MP 16.0 and R 4.4.2 statistical software. Continuous variables were compared with either the Student's *t*-test or the Mann–Whitney *U*-test, while categorical variables were assessed via the Chi-squared test or Fisher's exact test. PFS and OS were estimated through Kaplan-Meier curves and further analyzed using Log rank tests. The Forestplot package is used to visualize and interpret forest plots of overall survival subgroup analyses. The risk factors linked to overall survival were examined using both univariate and multivariate Cox proportional hazards models. To evaluate the stability of the Cox model results, 1000 bootstrap resamplings were performed on the raw data. Reconfigure the Cox proportional hazards model after each sampling and determine the hazard ratio (HR) and its confidence interval (CI). A two-tailed P value below 0.05 was considered statistically significant.

Results

Baseline Characteristics

Between January 2021 and October 2024, a total of 116 eligible patients were reviewed. After screening based on the inclusion and exclusion criteria, 88 patients for subsequent analysis were finally determined: 39 patients received CAE +HAIC and 49 patients received simple HAIC. Significant difference was found in the age between the two groups (mean

age 52.9 vs 58.2, P=0.019). No significant differences in other characteristics were observed. Following the PSM, a total of 31 patient pairs underwent evaluation (Figure 2). There was no statistically significant difference in any baseline characteristics between the two groups after the PSM. The equilibrium test and kernel density map indicated that the differential baseline characteristics of the two groups were balanced post-PSM, demonstrating a strong matching effect (Figure 3). A comprehensive comparison of the baseline characteristics between the two groups, both before and after PSM, is presented in Table 1.

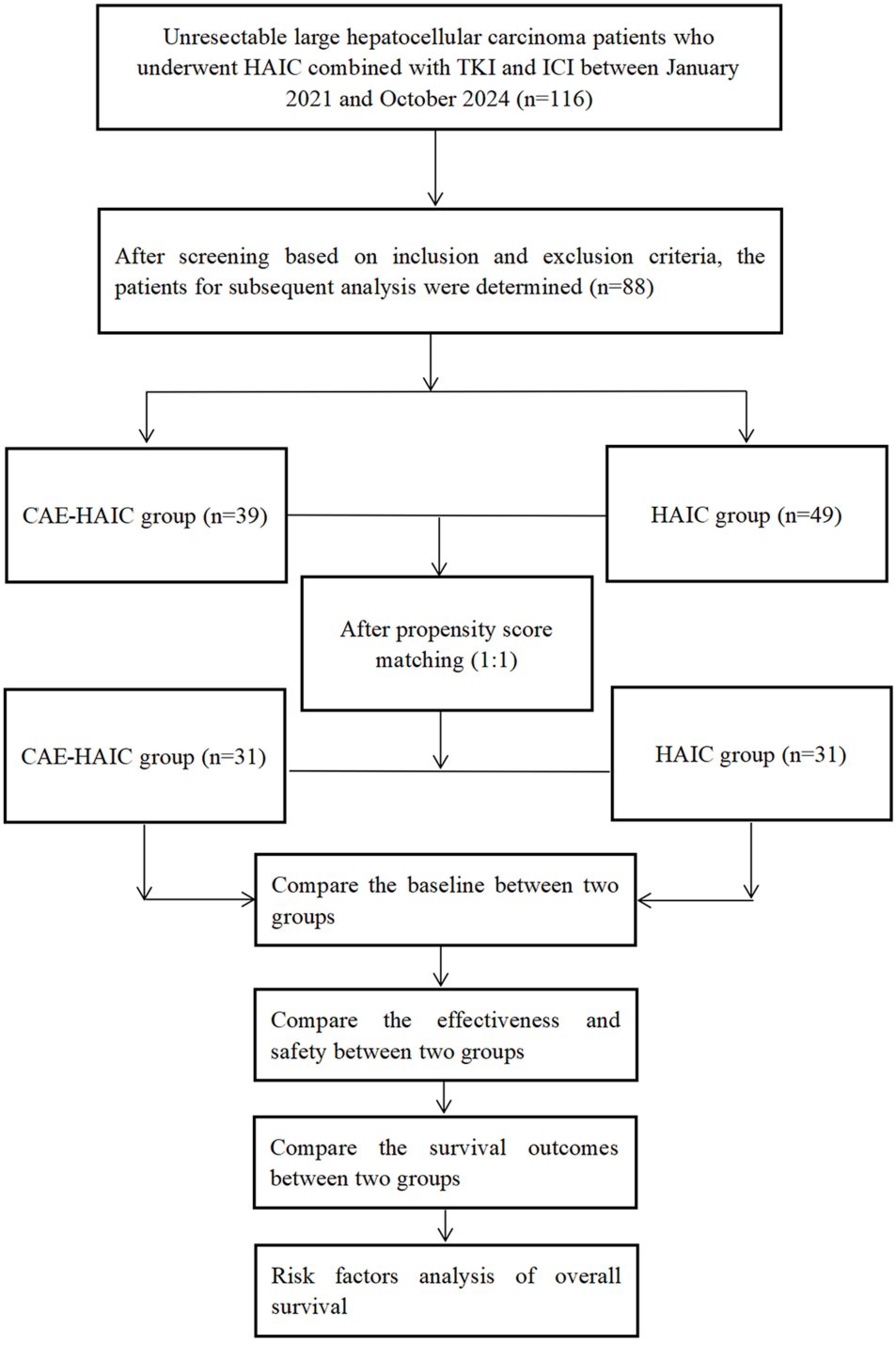

Figure 2 Research flowchart.

https://doi.org/10.2147/JHC.S546588

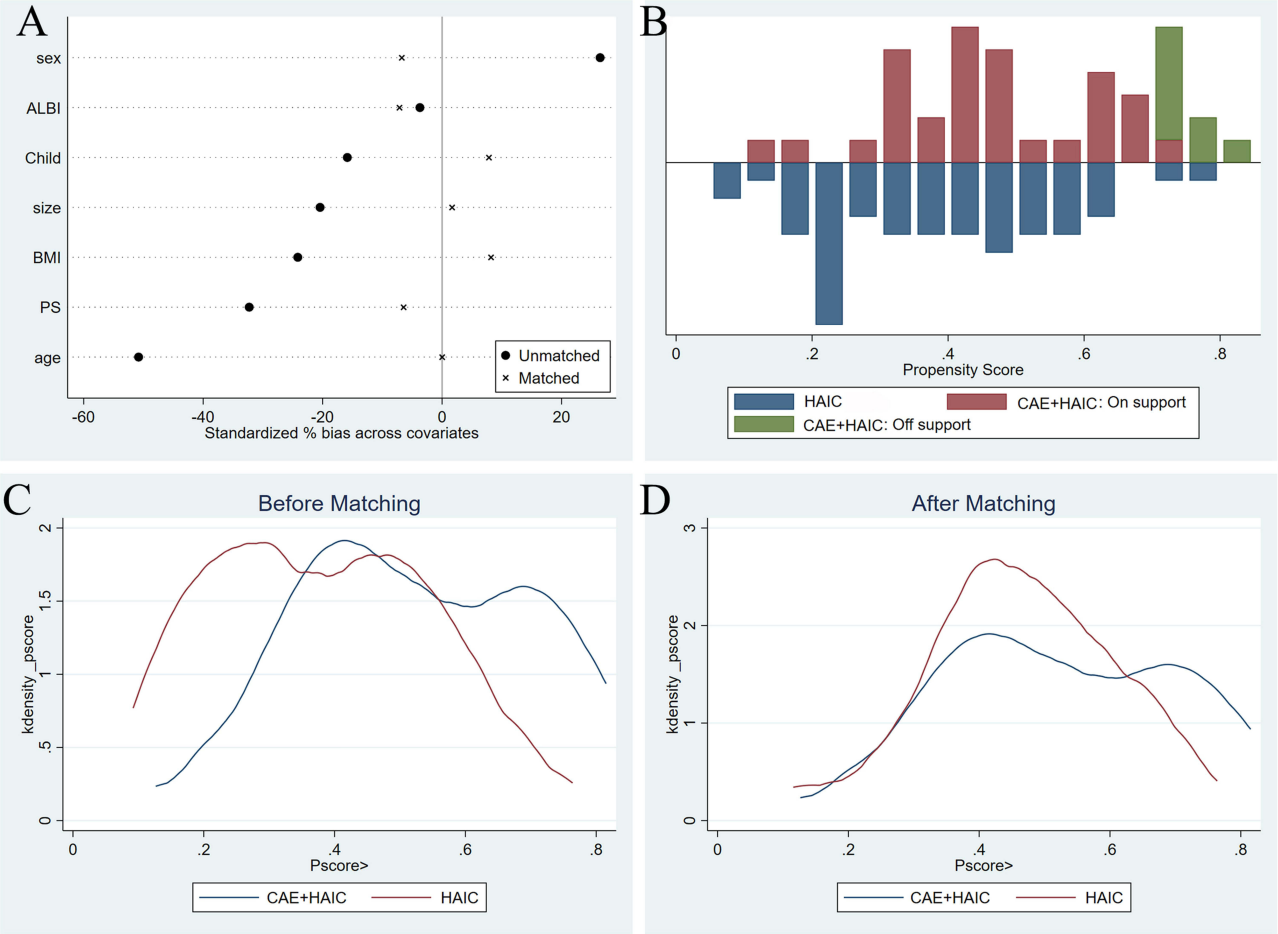

Figure 3 The results of propensity score matching; (**A**) The standardized deviation of difference features decreased significantly after matching; (**B**) After matching, the two groups have a preferable common value range; (**C**) The kernel density map before propensity score matching; (**D**) The kernel density map after propensity score matching. **Abbreviations**: CAE, collateral artery embolism; HAIC, hepatic artery infusion chemotherapy; PS, performance status; BMI, body mass index; ALBI, Albumin-bilirubin.

Tumour Response and Treatment-Related Adverse Events

All patients who participated in the study successfully completed the follow-up. The details regarding tumor response and treatment-related adverse events for these patients are presented in Table 2. The waterfall maps of tumor enhancement area changes after treatment were used to display tumor response rate between the two groups before and after PSM

Table 1 The Baseline Characteristics of Unresectable Huge Hepatocellular Carcinoma Patients Who Underwent HAIC

Variables	Before PSM			After PSM		
	CAE+HAIC (n = 39)	HAIC (n = 49)	P	CAE+HAIC (n = 31)	HAIC (n = 31)	P
Gender, n (%)			0.219			0.783
Male	28 (71.8)	29 (59.2)		21 (67.7)	22 (71.0)	
Female	11 (28.2)	20 (40.8)		10 (32.3)	9 (29.0)	
Age, Mean±SD	52.9±11.0	58.2±9.9	0.019*	55.8±9.7	55.8±10.0	1.000
BMI (kg/m^2), Mean±SD	21.8±2.3	22.4±2.6	0.267	22.1±2.4	21.9±2.2	0.733
Viral hepatitis B, n (%)	26 (66.7)	35 (71.4)	0.630	20 (64.5)	21 (67.7)	0.788
Cirrhosis, n (%)	28 (71.8)	31 (63.3)	0.398	22 (71.0)	19 (61.3)	0.421

(*Continued*)

Table 1 (Continued).

Variables	Before PSM			After PSM		
	CAE+HAIC (n = 39)	HAIC (n = 49)	P	CAE+HAIC (n = 31)	HAIC (n = 31)	P
ECOG score			0.133			0.799
0	23 (59.0)	21 (42.9)		17 (54.8)	16 (51.6)	
1-2	16 (41.0)	28 (57.1)		14 (45.2)	15 (48.4)	
Child-Pugh class, n (%)			0.459			0.740
A (5–6)	32 (82.1)	37 (75.5)		25 (80.6)	26 (83.9)	
B (7–9)	7 (17.9)	12 (24.5)		6 (19.4)	5 (16.1)	
ALBI, n (%)			0.861			0.776
1 (≤-2.60)	11 (28.2)	13 (26.5)		9 (29.0)	8 (25.8)	
2 (−2.60~-1.39)	28 (71.8)	36 (73.5)		22 (71.0)	23 (74.2)	
Tumor diameter(cm), Mean±SD	12.9±1.8	13.3±2.1	0.349	13.1±1.8	13.1±1.8	0.944
Vascular invasion, n (%)	11 (28.2)	19 (38.8)	0.299	9 (29.0)	11 (35.5)	0.587
Single tumor, n (%)	27 (69.2)	30 (61.2)	0.435	20 (64.5)	22 (71.0)	0.587
Tumor capsule, n (%)	25 (64.1)	27 (55.1)	0.394	19 (61.3)	16 (51.6)	0.442
AFP >400ng/mL, n (%)	21 (53.8)	23 (46.9)	0.520	16 (51.6)	13 (41.9)	0.445
TB (umol/L), Median (Q1, Q3)	15.1 (11.2, 19.3)	16.2 (11.9, 24.5)	0.460	16.7 (11.2, 19.9)	16 (9.9, 24.5)	1.000
Pre-albumin (mg/L), Mean±SD	183.6±58.9	163.2±65.8	0.133	180.9±62.7	175.8±59.3	0.743
Albumin (g/L), Mean±SD	37.1±4.0	37.4±4.7	0.732	37.1±4.3	37.7±3.8	0.548
ALT (U/L), Median (Q1, Q3)	34 (51, 84)	47 (31.5, 71)	0.406	53 (37, 84)	47 (37, 88)	0.632
AST (U/L), Median (Q1, Q3)	71 (52, 117)	75 (51, 97)	0.880	72 (52, 158)	73 (52, 105)	0.784
LDH (U/L), Median (Q1, Q3)	229 (198, 288)	235 (205, 305)	0.328	254 (198, 298)	223 (205, 369)	0.789
HAIC cycle, Mean±SD	3.3±1.4	3.3±1.3	0.939	3.3±1.4	3.3±1.2	0.847
HAIC regimen			0.945			0.799
RALOX	17 (43.6)	21 (42.9)		15 (48.4)	14 (45.2)	
FOLFOX	22 (56.4)	28 (57.1)		16 (51.6)	17 (54.8)	
Systemic therapy plan			0.377			0.309
Apatinib and Camrelizumab	17 (43.6)	26 (53.1)		13 (41.9)	17 (54.8)	
Lenvatinib and Tislelizumab	22 (56.4)	23 (46.9)		18 (58.1)	14 (45.2)	

Note: *The difference is statistically significant.

Abbreviations: CAE, Collateral artery embolism; HAIC, hepatic artery infusion chemotherapy; PSM, Propensity score matching; BMI, Body Mass Index; RALOX:Oxaliplatin plus Rituximab; FOLFOX: Oxaliplatin + Leucovorin + Fluorouracil; ALBI, Albumin-bilirubin; TB, Total bilirubin; ALT, Alanine asninotrasferase; AST, Aspartic transaminase; AFP, Alpha-fetoprotein; LDH, Lactic dehydrogenase; SD, Standard deviations.

Table 2 Comparison of Effectiveness and Safety Between the CAE+HAIC Group and the HAIC Group

Variables	Before PSM			After PSM		
	CAE+HAIC (n = 39)	HAIC (n = 49)	P	CAE+HAIC (n = 31)	HAIC (n = 31)	P
Initial tumor response			0.006*			0.044*
Complete response (CR)	2 (5.1)	1 (2.0)		2 (6.5)	1 (3.2)	
Partial response (PR)	25 (64.1)	19 (38.8)		21 (67.7)	14 (45.2)	
Stable disease (SD)	10 (25.6)	21 (42.9)		6 (19.4)	12 (38.7)	
Progressive disease (PD)	2 (5.1)	8 (16.3)		2 (6.5)	4 (12.9)	
Objective response rate, n (%)	27 (69.2)	20 (40.8)	0.008*	23 (74.2)	15 (48.4)	0.037*
Disease control rate, n (%)	37 (94.9)	41 (83.7)	0.191	29 (93.5)	27 (87.1)	0.668
Surgical resection, n (%)	6 (15.4)	5 (10.2)	0.685	5 (16.1)	4 (12.9)	1.000
Metastasis, n(%)	14 (35.9)	17 (34.7)	0.907	10 (32.3)	13 (41.9)	0.430
Deadline death, n(%)	26 (66.7)	33 (67.3)	0.946	20 (64.5)	16 (51.6)	0.303

(*Continued*)

Table 2 (Continued).

Variables	Before PSM			After PSM		
	CAE+HAIC (n = 39)	HAIC (n = 49)	P	CAE+HAIC (n = 31)	HAIC (n = 31)	P
Treatment-related adverse events						
At least once, n(%)	34 (87.2)	40 (81.6)	0.480	26 (83.9)	23 (74.2)	0.349
Severe adverse events, n (%)	4 (10.3)	5 (10.2)	1.000	4 (12.9)	3 (9.7)	1.000
Fever, n(%)	15 (38.5)	17 (34.7)	0.715	11 (35.5)	10 (32.3)	0.788
Abdominal pain, n (%)	29 (74.4)	23 (46.9)	0.009*	22 (71.0)	13 (41.9)	0.021*
Gastrointestinal symptoms, n (%)	17 (43.6)	22 (44.9)	0.902	14 (45.2)	13 (41.9)	0.798
Elevated transaminase, n (%)	15 (38.5)	21 (42.9)	0.677	10 (32.3)	12 (38.7)	0.596
Elevated bilirubin, n (%)	6 (15.4)	11 (22.4)	0.404	3 (9.7)	6 (19.4)	0.471
Gastrointestinal hemorrhage, n (%)	4 (10.3)	4 (8.2)	1.000	4 (12.9)	3 (9.7)	1.000
Myelosuppression, n (%)	11 (28.2)	17 (34.7)	0.516	7 (22.6)	10 (32.3)	0.393
Dermatitis, n (%)	12 (30.8)	18 (36.7)	0.558	9 (29.0)	9 (29.0)	1.000
Hypothyroidism, n (%)	12 (30.8)	17 (34.7)	0.697	9 (29.0)	10 (32.3)	0.783

Note: *The difference is statistically significant.
Abbreviations: CAE, Collateral artery embolism; HAIC, Hepatic artery infusion chemotherapy; PSM, Propensity score matching.

(Figure 4). There were statistically significant differences in the initial tumor response (P=0.006; P=0.044) and ORR between the two groups, both before and after PSM (Before [ORR: 69.2% vs 40.8%, P=0.008]; After [ORR: 74.2% vs 48.4%, P=0.037]). No statistically significant differences were observed in the DCR, surgical resection rate, metastasis rate, and mortality between the two groups, both before and after PSM.

No patients discontinued treatment or succumbed to treatment-related adverse events within a period of thirty days. Seventy-four out of all patients (84.1%) experienced at least one treatment-related adverse event. The most common treatment-related adverse events among these patients included abdominal pain (52/88, 59.1%), gastrointestinal

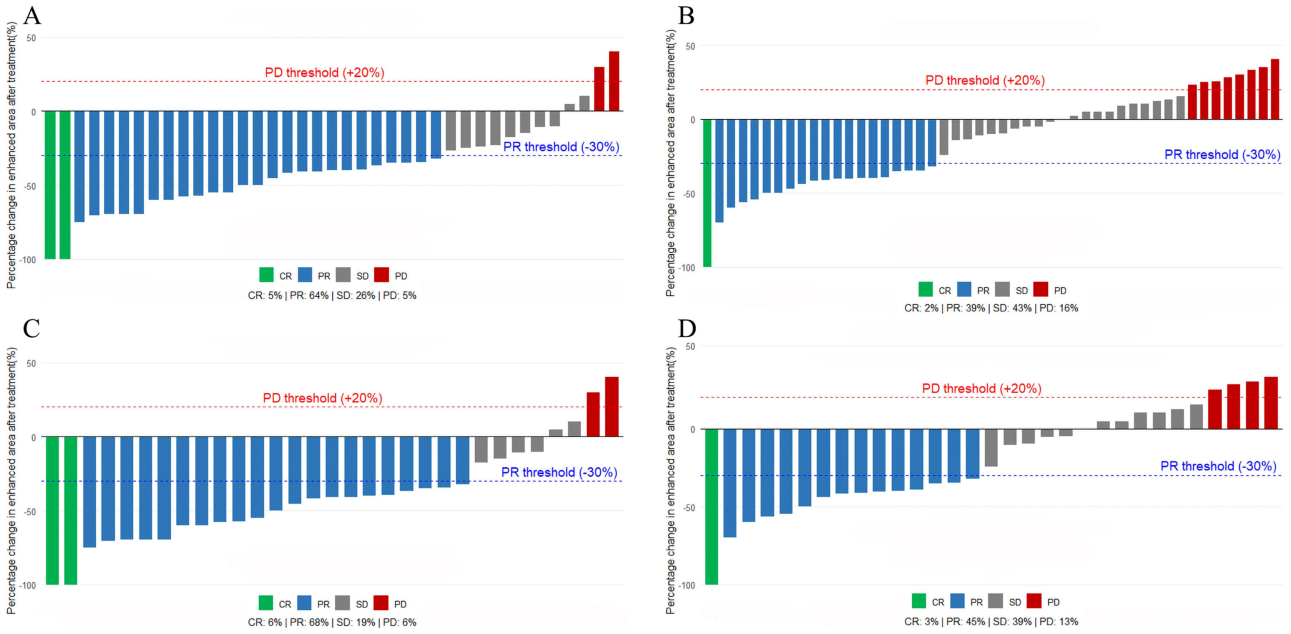

Figure 4 Waterfall plot for the best percentage change in tumor enhancement area after treatment for six weeks based on the modified Response Evaluation Criteria in Solid Tumors; (**A**) Tumor changes in the CAE-HAIC group before propensity score matching; (**B**) Tumor changes in the HAIC group before propensity score matching; (**C**) Tumor changes in the CAE-HAIC group after propensity score matching; (**D**) Tumor changes in the HAIC group after propensity score matching.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

symptoms (39/88, 44.3%), elevated transaminase levels (36/88, 40.9%), fever (32/88, 36.4%), and dermatitis (30/88, 34.1%). The overall incidence of severe adverse events was 10.2% (9/88). Compared with the "HAIC" group, the incidence of abdominal pain was higher in the "CAE+HAIC" group, both before and after PSM (Before: 74.7% vs 46.9%, P=0.009; After: 71.0% vs 41.9%, P=0.021). There were no significant differences in the rates of other treatment-related adverse events or severe adverse events between the two groups, both before and after PSM. Table 2 summarizes the treatment-related adverse events for both groups, both before and after PSM.

Survival Analysis

Before PSM, the median PFS in the "CAE+HAIC" group was 12.7 months, compared to 6.5 months in the "HAIC" group (HR=0.445; 95% CI: 0.268–0.740; P=0.002; Figure 5A). The median OS in the "CAE+HAIC" group was 14.9 months, compared to 12.5 months in the "HAIC" group (HR=0.357; 95% CI: 0.194–0.656; P<0.001; Figure 5B). After PSM, the median PFS in the "CAE+HAIC" group was 13.5 months, compared to 7.8 months in the "HAIC" group (HR=0.475; 95% CI: 0.252–0.895; P=0.021; Figure 5C). The median OS in the "CAE+HAIC" group was 15.5 months, compared to 12.5 months in the "HAIC" group (HR=0.439; 95% CI: 0.199–0.970; P=0.042; Figure 5D).

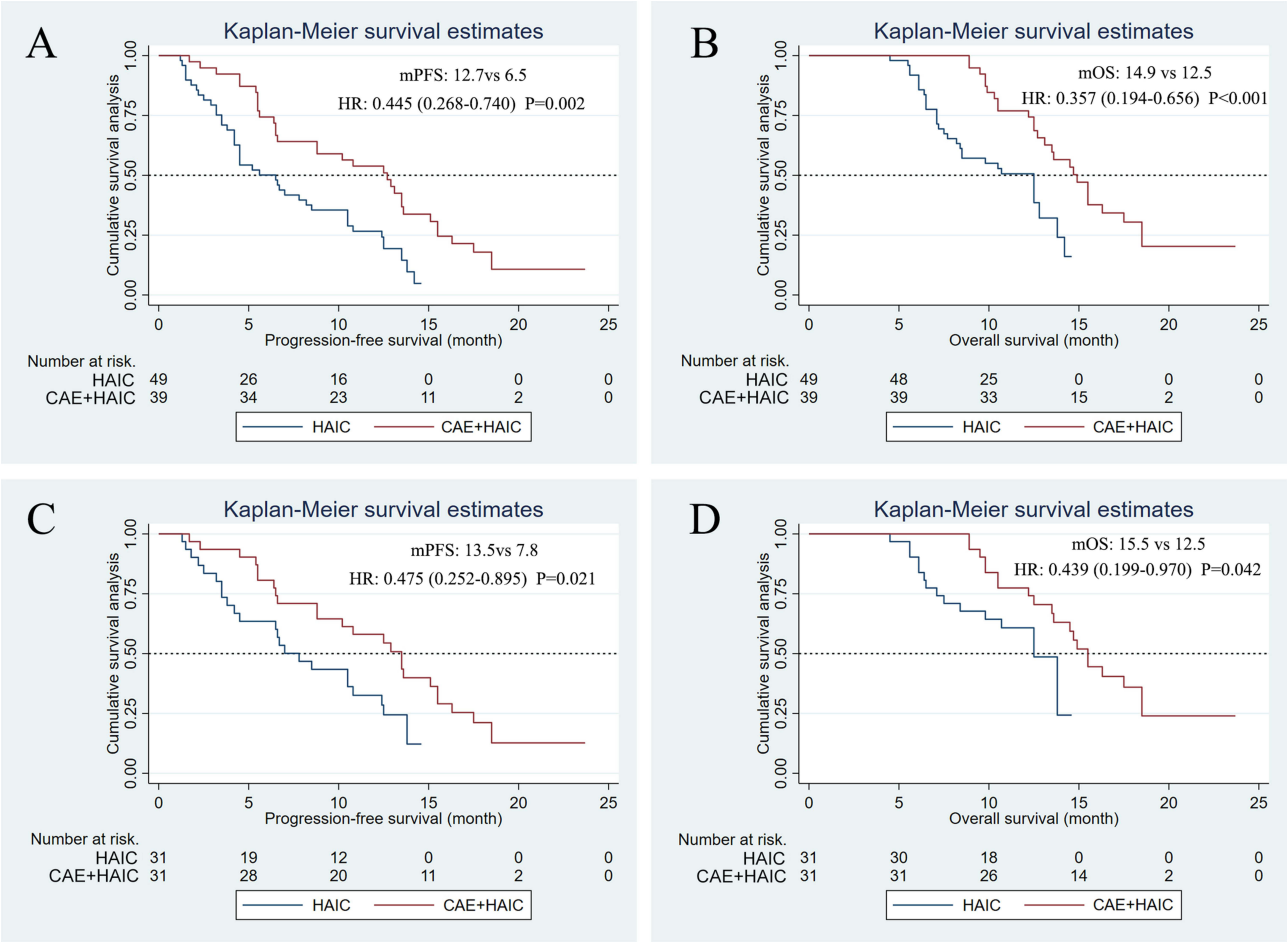

Figure 5 Kaplan–Meier curves of survival outcome between two groups; (**A**) Comparison of progression free survival between the two groups before propensity score matching; (**B**) Comparison of overall survival between the two groups before propensity score matching; (**C**) Comparison of progression free survival between the two groups after propensity score matching; (**D**) Comparison of overall survival between the two groups after propensity score matching.

Abbreviations: CAE, collateral artery embolism; HAIC, hepatic artery infusion chemotherapy; HR, hazard ratio; mPFS, median progression free survival; mOS, median overall survival.

https://doi.org/10.2147/JHC.S546588

Overall Survival Subgroup Analysis

Figure 6 shows the overall survival benefits of CAE+HAIC across significant subgroups. The forest plot indicated that the "CAE+HAIC" group significantly reduced the risk of death by 64% compared to the "HAIC" group in the overall population (HR=0.36, 95% CI 0.19–0.66). However, the following subgroups did not demonstrate significant benefits: age >60 (HR=0.27, 95% CI: 0.06–1.23), female (HR=0.44, 95% CI: 0.17–1.15), other hepatitis (HR=0.70, 95% CI: 0.23–2.09), non-cirrhosis (HR=0.55, 95% CI: 0.19–1.61), PS=0 (HR=0.49, 95% CI: 0.19–1.26), multiple tumors (HR=0.50, 95% CI: 0.22–1.13), lack of tumor capsule (HR=0.44, 95% CI: 0.19–1.02), AFP >400 (HR=0.51, 95% CI: 0.23–1.12), and FOLFOX-HAIC (HR=0.73, 95% CI: 0.36–1.45). Furthermore, the RALOX-HAIC subgroup demonstrated the best overall survival advantage (HR=0.08, 95% CI: 0.02–0.36).

Risk Factors Analysis of OS

The result of the univariate Cox proportional hazards model analysis revealed that gender, RALOX-HAIC, CAE, PS≥1, Child-Pugh class, single tumor, prealbumin levels <180 mg/L, and lactic dehydrogenase (LDH) levels >245 U/L were the risk factors of OS for unresectable huge HCC patients who initially underwent HAIC combined with TKI and ICI. The result of multivariate Cox proportional hazards model analysis showed that CAE (HR=0.403, 95% CI: 0.213–0.762; P=0.005), prealbumin levels <170 mg/L (HR=2.195, 95% CI: 1.226–3.929; P=0.008), and LDH levels >245 U/L (HR=2.136, 95% CI: 1.215–3.757; P=0.008) were independent risk factors of OS. Bootstrap analysis further reassured the stability of these effects, showing that CAE (HR=0.390, 95% CI: 0.173–0.716; P=0.011), prealbumin <180 mg/L

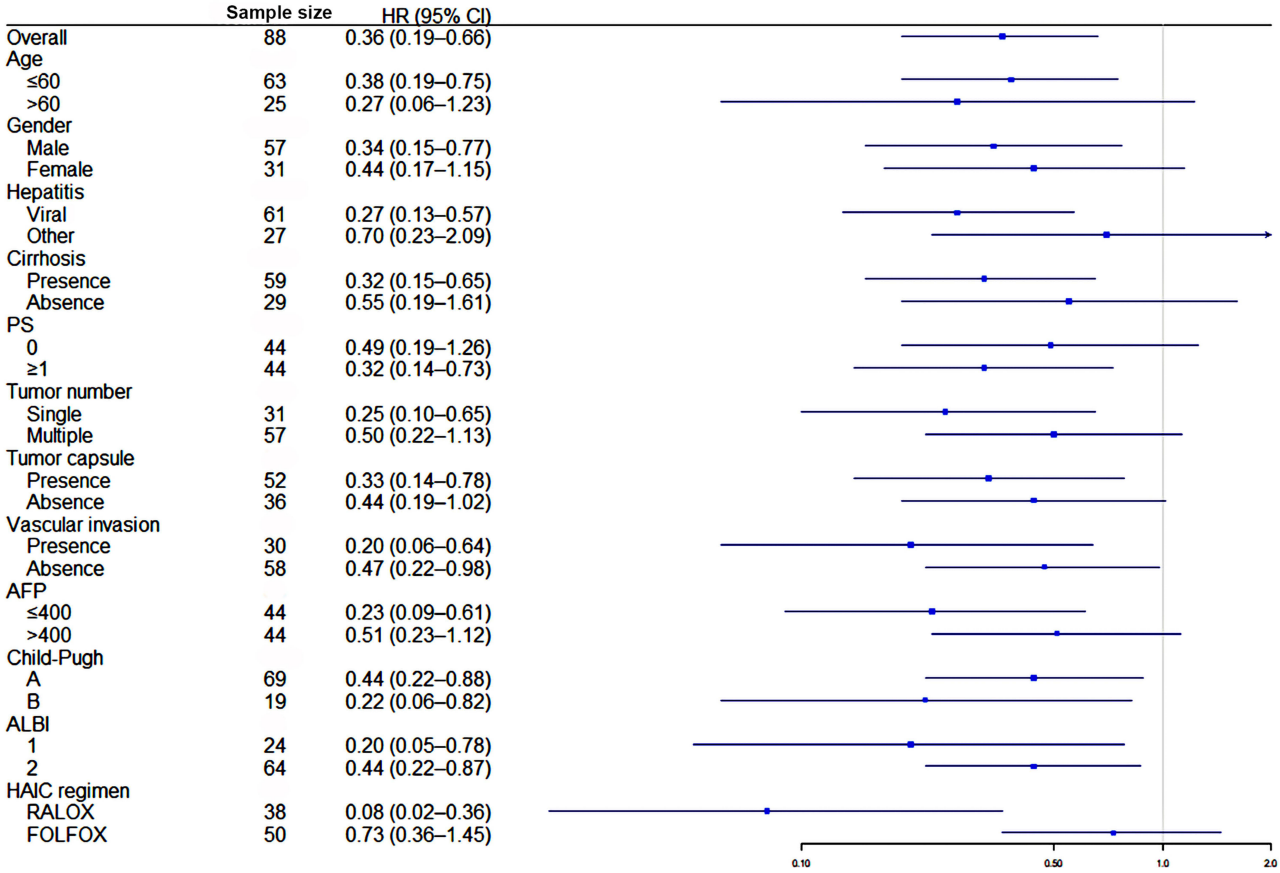

Figure 6 The forest plot of the overall survival subgroup analysis between the CAE+HAIC group and the HAIC group.

Abbreviations: CAE, collateral artery embolism; HAIC, hepatic artery infusion chemotherapy; HR, hazard ratio; CI, Confidence interval; HAIC, hepatic artery infusion chemotherapy; PS, performance status; ALBI, Albumin-bilirubin; AFP, alpha-fetoprotein; RALOX:Oxaliplatin plus Rituximab; FOLFOX: Oxaliplatin + Leucovorin + Fluorouracil.

Table 3 Univariate and Multivariate Cox Analyses to Evaluate the Predictors for Overall Survival

	Univariate Analysis		Multivariate Analysis		Bootstrap (n=1000)	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Gender	0.531 (0.313–0.901)	0.019*	0.627 (0.355–1.108)	0.108	0.618 (0.294–1.173)	0.185
Age	0.995 (0.969–1.020)	0.675				
BMI	0.979 (0.869–1.104)	0.734				
HAIC cycle	0.884 (0.732–1.067)	0.198				
RALOX-HAIC	0.487 (0.274–0.865)	0.014*	0.607 (0.325–1.133)	0.117	0.630 (0.256–1.202)	0.193
CAE	0.357 (0.194–0.656)	0.001*	0.403 (0.213–0.762)	0.005*	0.390 (0.173–0.716)	0.011*
Systemic therapy	1.095 (0.706–1.699)	0.685				
Viral hepatitis	1.333 (0.749–2.370)	0.328				
Cirrhosis	0.888 (0.513–1.537)	0.671				
ECOG score≥1	2.119 (1.252–3.585)	0.005*	1.168 (0.528–2.582)	0.703	1.303 (0.504–2.856)	0.719
Child-Pugh class	1.847 (1.035–3.296)	0.038*	1.050 (0.530–2.077)	0.890	1.100 (0.365–2.340)	0.917
ALBI	1.478 (0.805–2.712)	0.207				
Tumor diameter	0.999 (0.868–1.150)	0.985				
Vascular invasion	1.500 (0.888–2.534)	0.130				
Single tumor	0.504 (0.301–0.842)	0.009*	0.753 (0.336–1.689)	0.491	0.817 (0.265–1.829)	0.568
Tumor capsule	0.706 (0.421–1.183)	0.186				
AFP >400ng/mL	1.155 (0.691–1.930)	0.583				
TB>17.1umol/L	1.026 (0.610–1.727)	0.922				
Albumin<35g/L	0.950 (0.549–1.643)	0.855				
Prealbumin<180mg/L	2.304 (1.367–3.881)	0.002*	2.195 (1.226–3.929)	0.008*	2.488 (1.151–4.866)	0.036*
ALT>40 U/L	0.856 (0.507–1.445)	0.560				
AST>40 U/L	0.709 (0.335–1.503)	0.370				
LDH>245 U/L	1.751 (1.042–2.943)	0.035*	2.136 (1.215–3.757)	0.008*	2.475 (1.183–4.677)	0.024*

Note: *The p-value is statistically significant.

Abbreviations: BMI, Body Mass Index; CAE, Collateral artery embolism; HAIC, Hepatic artery infusion chemotherapy; RALOX:Oxaliplatin plus Rituximab; ALBI, Albumin-bilirubin; TB, Total bilirubin; ALT, Alanine asninotrasferase; AST, Aspartic transaminase; AFP, Alpha-fetoprotein; LDH, Lactic dehydrogenase; HR, Hazard Ratio; CI, Confidence interval.

(HR=2.488, 95% CI: 1.151–4.866; P=0.036), and LDH >245 U/L (HR=2.475, 95% CI: 1.183–4.677; P=0.024) have high stability in their effects. The comprehensive findings were presented in Table 3.

Discussion

For unresectable hepatocellular carcinoma, comprehensive treatment with TACE or HAIC is the main treatment plan.[11,18] Current research indicates that the FOLFOX-HAIC was a cost-effective option compared to TACE for patients with large unresectable HCC in China.[12] Huang et al found that DEB-TACE+HAIC combined with TKI and ICI is tolerable and effective in unresectable large or giant HCC patients.[19] The severe adverse events rate of DEB-TACE+HAIC is 37.7% (26/69) and ORR is 71.0%. We have developed a comprehensive multi-level CAE and HAIC, based on the Three-Stage Mixed Chemoembolic Regimen TACE, to ensure compatibility between therapeutic efficacy and the risk of damage. Compared with Huang's study, the severe adverse events rate of CAE+HAIC is lower (10.3% vs 37.7%) with similar ORR (69.2% vs 71.0%). The results revealed that the combination therapy of CAE and HAIC had better initial tumor response and ORR, longer OS and PFS than the HAIC therapy, but only increased the incidence of mild abdominal pain. The PSM also demonstrated consistent results, enhancing the stability and reliability of these findings. This combined treatment approach might provide a promising opportunity for unresectable HCC, improving tumor response and prolonging survival time. This offers a theoretical foundation for additional prospective clinical trials to verify the efficacy. Besides, the interesting observation that the mPFS (12.7m) and mOS (14.9m) are very close for the CAE+HAIC +TKI+ICI group is worth discussing. For huge HCC patients undergoing this combination therapy, once the tumor progresses, it often rapidly shortens the survival time due to aggressive tumor biology and treatment-resistant. Of course, this also indirectly reflects that the combination therapy has slowed down tumor progression and improved PFS.

Additionally, the results of the subgroup analysis on overall survival deserve discussion. Although CAE reduced the overall survival risk by 64% in the total HAIC treatment population, some subgroups still did not show significant benefits. It means that the patient's essential information, including age, gender, hepatitis type, cirrhosis condition, performance status, and tumor's characteristics should be taken into account before starting combination therapy. For single-tumor HCC with a tumor capsule and low AFP, the combination of CAE and HAIC may provide significant benefits. This establishes a theoretical foundation for developing predictive models that identify populations likely to benefit from this combination treatment. It's great to highlight that CAE combined with RALOX-HAIC showed the most promising overall survival advantage. On the other hand, CAE combined with FOLFOX-HAIC did not demonstrate significant survival benefits. This could be linked to the half-life of chemotherapy medications. Raltitrexed, a folate analog antimetabolite that targets thymidylate synthase,[20] has a significantly longer plasma half-life of 198 hours compared to 5-fluorouracil.[21] A recent study showed that the combination of RALOX-HAIC and lenvatinib yields superior survival outcomes and enhanced tolerability in elderly patients with unresectable HCC compared to TACE alone.[22] Our previous research has also confirmed that RALOX-HAIC has comparable efficacy to FOLFOX-HAIC in liver cancer patients with portal vein thrombosis, but with fewer adverse reactions.[23] After collateral artery embolization, drugs remain in the tumor for a longer duration, so medications with extended half-lives are likely to yield better therapeutic effects. This could illustrate the possible mechanism for the optimal clinical effectiveness of the RALOX perfusion regimen following CAE. However, it is important to pay attention to the toxicity differences between these regimens, especially in the context of CAE. Certainly, these results represent exploratory findings rather than conclusive evidence and necessitate prospective, randomized, controlled trials for verification.

The results of risk factor analysis are also worth discussing. This study ultimately identified CAE, prealbumin levels <180 mg/L, and LDH levels >245 U/L as independent factors for OS. Given the limited sample size, a bootstrap analysis was employed to enhance the robustness of the results. The results showed that the Cox proportional hazards model had good robustness. Prealbumin is a reliable indicator of nutritional status and inflammatory stress, with a short half-life, making it a sensitive biomarker for assessing morbidity, mortality, and tumor progression.[24,25] Studies have shown that low preoperative serum prealbumin levels correlate with poor long-term survival rates post-liver resection in hepatocellular carcinoma patients.[26] A recent study indicated that low preoperative prealbumin levels are strongly correlated with a poor prognosis in patients with unresectable HCC after undergoing TACE.[27] Our study indicated that prealbumin levels <180 mg/L correlated with poor overall survival in unresectable HCC patients who underwent HAIC and systemic therapy. LDH regulates tumor development by influencing the tumor's biochemical environment, significantly affecting cell invasion, immunosuppression, angiogenesis, and metastasis.[28] Previous research indicates that elevated preoperative serum LDH levels in HCC patients are associated with a worse prognosis, including reduced survival and increased recurrence rates.[29,30] The monitoring of tumor LDH levels may be utilized for the purpose of prognosis stratification. Our study found that LDH levels >245 U/L correlated with poor overall survival in unresectable HCC patients who underwent HAIC and systemic therapy.

This research has some limitations as well. This study was a retrospective analysis conducted at a single center, featuring a limited sample size and short follow-up period. Although propensity score matching and bootstrap analysis were employed to strengthen the study's validity, these research results are still exploratory. Further prospective clinical studies with larger sample sizes and longer follow-up durations are necessary to confirm these results. The retrospective study did not clearly explain the potential mechanisms underlying the combination therapy. We speculate that complete collateral embolization will reduce tumor blood supply, which increases the concentration of chemotherapy drugs. It achieves the effect of increasing local drug concentration without causing severe reactions such as rapid necrosis of the tumor embolism. Additional research is necessary to elucidate these potential mechanisms of action. The analysis of risk factors for overall survival was exploratory. Therefore, confirmatory studies are necessary to validate these findings. In addition, in this study, traditional tumor factors like liver function and AFP levels did not show significant prognostic value, likely due to the small sample size and high tumor heterogeneity in huge HCC patients. All patients received standardized treatment combining HAIC with TKI and ICI, which may have reduced the impact of tumor characteristics. More research is needed to explore how tumor features affect prognosis.

Conclusion

This study found that a multi-level comprehensive CAE sequential HAIC, combined with TKI and ICI, can improve tumor response and prolong survival time in unresectable huge HCC patients while remaining safe and tolerable. In unresectable huge HCC patients treated with HAIC and systemic therapy, CAE, prealbumin levels <180 mg/L, and LDH levels >245 U/L were identified as independent factors affecting overall survival.

Data Sharing Statement

All data generated or analyzed during this study is included in this published article.

Acknowledgment

The authors thank everyone who contributed to this article.

Funding

This research was supported by the "Sponsored by Joint project of Chongqing Health Commision and Science and Technology Bureau" (2025ZYYB017), "Interventional Therapy Clinical Special Research of Chengdu High-Tech Medical Association" (2024019), and "Chongqing University Jiangjin Hospital Internal Cultivation Project" (2023YUCXM001, 2024LCXM002).

Disclosure

The authors declare no competing interests.

References

1. Singh SP, Madke T, Chand P. Global epidemiology of hepatocellular carcinoma. *J Clin Exp Hepatol*. 2025;15(2):102446. doi:10.1016/j.jceh.2024.102446
2. Zhou J, Sun H, Wang Z, et al. Guidelines for the diagnosis and treatment of primary liver cancer (2022 edition). *Liver Cancer*. 2023;12(5):405–444. doi:10.1159/000530495
3. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681–693. doi:10.1016/j.jhep.2021.11.018
4. Guo BJ, Ruan Y, Wang YJ, et al. Jiedu recipe, a compound Chinese herbal medicine, inhibits cancer stemness in hepatocellular carcinoma via Wnt/β-catenin pathway under hypoxia. *J Integr Med*. 2023;21(5):474–486. doi:10.1016/j.joim.2023.06.008
5. Brown ZJ, Tsilimigras DI, Ruff SM, et al. Management of hepatocellular carcinoma: a review. *JAMA Surgery*. 2023;158(4):410–420. doi:10.1001/jamasurg.2022.7989
6. Piscaglia F, Masi G, Martinelli E, et al. Atezolizumab plus bevacizumab as first-line treatment of unresectable hepatocellular carcinoma: interim analysis results from the phase IIIb AMETHISTA trial. *ESMO Open*. 2025;10(2):104110. doi:10.1016/j.esmoop.2024.104110
7. Sangro B, Chan SL, Kelley RK, et al. Four-year overall survival update from the Phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *Annals Oncol*. 2024;35(5):448–457. doi:10.1016/j.annonc.2024.02.005
8. Wu J, Liu W, Qiu X, et al. A noninvasive approach to evaluate tumor immune microenvironment and predict outcomes in hepatocellular carcinoma. *Phenomics*. 2023;3(6):549–564. doi:10.1007/s43657-023-00136-8
9. Sergio A, Cristofori C, Cardin R, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. *Am J Gastroenterol*. 2008;103(4):914–921. doi:10.1111/j.1572-0241.2007.01712.x
10. Zhao M, Guo Z, Zou YH, et al. Arterial chemotherapy for hepatocellular carcinoma in China: consensus recommendations. *Hepatol Internat*. 2024;18(1):4–31. doi:10.1007/s12072-023-10599-6
11. Jiang P, Chen C, Tian J, et al. Efficacy and safety of HAIC-FOLFOX plus tyrosine kinase inhibitors and immune checkpoint inhibitors as first-line treatment for unresectable advanced hepatocellular carcinoma: a systematic review and meta-analysis. *Acad Radiol*. 2024;2024:1.
12. Zhang H, Zeng X, Peng Y, Tan C, Wan X. Cost-effectiveness analysis of hepatic arterial infusion chemotherapy of infusional fluorouracil, leucovorin, and oxaliplatin versus transarterial chemoembolization in patients with large unresectable hepatocellular carcinoma. *Front Pharmacol*. 2022;13:849189. doi:10.3389/fphar.2022.849189
13. Liu H, Wang C, Wang R, et al. New insights into mechanisms and interventions of locoregional therapies for hepatocellular carcinoma. *Chin J Cancer Res = Chung-Kuo Yen Cheng Yen Chiu*. 2024;36(2):167–194. doi:10.21147/j.issn.1000-9604.2024.02.06
14. Cai M, Liang L, Zhang J, et al. Lenvatinib plus drug-eluting bead transarterial chemoembolization with/without hepatic arterial infusion chemotherapy for hepatocellular carcinoma larger than 7 cm with major portal vein tumor thrombosis: a multicenter retrospective cohort study. *Int J Surg*. 2024;110(12):7860–7870. doi:10.1097/JS9.0000000000001819
15. Yang Y, Du N, Ma J, et al. Efficacy and safety of transarterial chemoembolization with a three-stage mixed chemoembolic regimen for large unresectable hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2023;10:1897–1910. doi:10.2147/JHC.S433409
16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. doi:10.1016/j.ejca.2008.10.026

17. Gilbert A, Piccinin C, Velikova G, et al. Linking the European organisation for research and treatment of cancer item library to the common terminology criteria for adverse events. *J clin oncol*. 2022;40(32):3770–3780. doi:10.1200/JCO.21.02017
18. Xie DY, Zhu K, Ren ZG, Zhou J, Fan J, Gao Q. A review of 2022 Chinese clinical guidelines on the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary surg nutr*. 2023;12(2):216–228. doi:10.21037/hbsn-22-469
19. Huang J, Huang W, Zhan M, et al. Drug-eluting bead transarterial chemoembolization combined with FOLFOX-based hepatic arterial infusion chemotherapy for large or huge hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2021;8:1445–1458. doi:10.2147/JHC.S339379
20. Surmont VF, van Meerbeeck JP. Raltitrexed in mesothelioma. *Expert Rev Anticancer Ther*. 2011;11(10):1481–1490. doi:10.1586/era.11.136
21. Blair EY, Rivory LP, Clarke SJ, McLachlan AJ. Population pharmacokinetics of raltitrexed in patients with advanced solid tumours. *Br J Clin Pharmacol*. 2004;57(4):416–426. doi:10.1111/j.1365-2125.2003.02050.x
22. Lu H, Gao Y, Xia X, Fu Q, Xiang D. RALOX-HAIC (raltitrexed + oxaliplatin) combined with lenvatinib improves survival and safety in elderly patients with unresectable hepatocellular carcinoma. *BMC Cancer*. 2025;25(1):882. doi:10.1186/s12885-025-14274-x
23. Tan HY, Liu SQ, Liu YH, Dai GH, Zheng JL, Feng HG. Radiotherapy, tyrosine kinase inhibitors, immune checkpoint inhibitors combined with hepatic arterial infusion chemotherapy of RALOX versus FOLFOX for hepatocellular carcinoma with portal vein tumor thrombus: a propensity score-matching cohort study. *Discov Oncol*. 2025;16(1):717. doi:10.1007/s12672-025-02553-9
24. Yang F, Wei L, Huo X, Ding Y, Zhou X, Liu D. Effects of early postoperative enteral nutrition versus usual care on serum albumin, prealbumin, transferrin, time to first flatus and postoperative hospital stay for patients with colorectal cancer: a systematic review and meta-analysis. *Contemp Nurse*. 2018;54(6):561–577. doi:10.1080/10376178.2018.1513809
25. Zhen WC, Sun J, Bai XT, et al. Trends of alkaline phosphatase to prealbumin ratio in patients with hepatitis B linked to hepatocellular carcinoma development. *World J Gastroenterol*. 2025;31(2):99349. doi:10.3748/wjg.v31.i2.99349
26. Liao YY, Teng CL, Peng NF, et al. Serum prealbumin is negatively associated with survival in hepatocellular carcinoma patients after hepatic resection. *J Cancer*. 2019;10(13):3006–3011. doi:10.7150/jca.30903
27. Lei K, Wang JG, Li Y, et al. Prognostic value of preoperative prealbumin levels in patients with unresectable hepatocellular carcinoma undergoing transcatheter arterial chemoembolisation. *Heliyon*. 2023;9(8):e18494. doi:10.1016/j.heliyon.2023.e18494
28. Jin H, Liu Q, Li J, Zhao S, Tuo B. Multifaceted roles of lactate dehydrogenase in liver cancer (Review). *Int J Oncol*. 2025;66(6):1–11. doi:10.3892/ijo.2025.5756
29. Su K, Huang W, Li X, et al. Evaluation of lactate dehydrogenase and alkaline phosphatase as predictive biomarkers in the prognosis of hepatocellular carcinoma and development of a new nomogram. *J Hepatocell Carcinoma*. 2023;10:69–79. doi:10.2147/JHC.S398632
30. Wu SJ, Lin YX, Ye H, Xiong XZ, Li FY, Cheng NS. Prognostic value of alkaline phosphatase, gamma-glutamyl transpeptidase and lactate dehydrogenase in hepatocellular carcinoma patients treated with liver resection. *Int J Surg*. 2016;36(Pt A):143–151. doi:10.1016/j.ijsu.2016.10.033