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Research

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

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Abstract

Background This retrospective study aimed to evaluate the safety and effectiveness of hepatic arterial infusion chemotherapy with raltitrexed and oxaliplatin (RALOX-HAIC) combined with radiotherapy, tyrosine kinase inhibitors, and immune checkpoint inhibitors in patients with hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT).

Methods A propensity score-matching (PSM) cohort study was conducted. The tumor response, treatment-related adverse events, survival outcomes were compared. Univariate and multivariate analyses were conducted to explore the risk factors of overall survival (OS).

Results Twenty-one pairs of patients were evaluated after PSM. No statistical differences were found in the tumor response, objective response rate, disease control rate, PVTT response, surgical resection rate, metastasis, and mortality between the two groups before and after PSM. Compared with the FOLFOX-HAIC group, the incidences of abdominal pain and fever was lower in the RALOX-HAIC group (P = 0.028, P = 0.029). These differences still had statistical significance after PSM (P = 0.013, P = 0.014). No statistical differences were found in OS and progression-free survival (PFS) between the two groups before and after PSM (Before [OS: hazard ratio(HR) = 1.138; 95%CI 0.569–2.276, P = 0.715; PFS: HR = 0.549; 95%CI 0.195–1.548, P = 0.257; After [OS: HR = 0.998; 95%CI 0.438–2.274, P = 0.995; PFS: HR = 0.792; 95%CI 0.359–1.748, P = 0.564]). The prealbumin < 170 mg/L before therapy was an independent risk factor for OS (HR = 2.234; 95%CI 1.051–4.751; P = 0.037).

Conclusions The RALOX-HAIC combined radiotherapy, TKI, and ICI may provide similar survival advantages with fewer treatment-related abdominal pain and fever compared to FOLFOX-HAIC for HCC patients with PVTT. The prealbumin < 170 mg/L before therapy is an independent risk factor for OS.

Keywords Hepatocellular carcinoma · Portal vein tumor thrombus · Hepatic artery infusion chemotherapy · Raltitrexed · Propensity score matching

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1 Introduction

Portal vein tumor thrombus (PVTT) frequently complicates hepatocellular carcinoma (HCC) and greatly deteriorates its prognosis [1]. Strategies for managing HCC with PVTT encompass a variety of methods, including surgical resection, transarterial chemoembolization, radiotherapy, tyrosine kinase inhibitors (TKI), immune checkpoint inhibitors (ICI), and various combination therapies [2, 3]. While international guidelines recommend ICI-based regimens, such as Atezolizumab plus bevacizumab or Tremelimumab plus durvalumab, as the first-line treatment for unresectable HCC with PVTT [4–6], more aggressive approaches have shown promise in improving outcomes [7]. Recent advancements in surgical techniques, radiotherapy, and systemic therapies have expanded the treatment options and improved the prognosis of HCC patients with PVTT [8]. However, there is still no global consensus on management, and treatment decisions should consider factors such as PVTT type, liver function, and patient performance status [9]. In recent years, the combination therapy of hepatic arterial infusion chemotherapy (HAIC) and radiotherapy has provided these patients with new treatment options.

Several studies have shown that radiotherapy combined with HAIC can yield promising results for the treatment of HCC with PVTT. Some studies have reported improved progression-free survival, overall survival, and disease control rates compared to sorafenib monotherapy [10, 11]. A meta-analysis revealed that combination therapy with radiotherapy and HAIC demonstrated better objective response rates for PVTT and primary liver tumors [12]. HAIC combined with radiotherapy is safe and tolerable with manageable adverse events [13, 14]. This approach may be particularly beneficial in patients with advanced HCC and PVTT. Our previous research has also shown that the combination therapy of HAIC and radiotherapy can improve overall survival and progression-free survival without increasing the occurrence of treatment-related complications in HCC patients with PVTT [15]. However, the current mainstream therapeutic regimen of HAIC treatment is 5-fluorouracil plus oxaliplatin (FOLFOX), and the arterial perfusion of 5-fluorouracil over 46 h is not comfortable or convenient [16]. The arterial perfusion chemotherapy regimen must be improved to enhance patient comfort and compliance without compromising efficacy. Although research has shown that the arterial perfusion of 5-fluorouracil shortened to 23 h in the FOLFOX-HAIC had similar tumor efficacy with lower rate of adverse reaction [17], the issue of drug half-life still needs to be considered.

Raltitrexed, compared to 5-fluorouracil, only requires shorter infusions to achieve a therapeutic effect because of its long half-life in the plasma. Studies have shown comparable effectiveness and safety between RALOX (raltitrexed plus oxaliplatin) and FOLFOX when combined with TKIs and ICIs for intermediate and advanced HCC [18]. Compared with TACE, RALOX-HAIC markedly improved the objective response rate of HCC with PVTT and prolonged survival without increasing the incidence rate of severe adverse events [19]. In transarterial chemoembolization for unresectable HCC, raltitrexed-based regimens showed higher progression-free survival compared than 5-fluorouracil-based regimens [20]. Previous studies have shown that radiotherapy can enhance the efficacy of chemotherapy drugs [21, 22]. Due to the long half-life of raltitrexed and short duration of RALOX-HAIC, patients can receive radiotherapy more quickly and maintain a higher blood drug concentration during treatment. It may improve the therapeutic effect. However, the efficacy and safety of RALOX-HAIC and radiotherapy for HCC patients with PVTT remain unknown.

Therefore, this retrospective cohort study aimed to evaluate the safety and tumor effectiveness of RALOX-HAIC and radiotherapy combined with ICI plus TKI for HCC patients with PVTT and to compare it with FOLFOX-HAIC after propensity score matching (PSM).

2 Materials and methods

2.1 Patients selection

This retrospective study gathered clinical information from patients with HCC and PVTT who received comprehensive treatment between January 2020 and October 2024. Eligible patients were stratified into two distinct cohorts according to their respective HAIC protocols: RALOX-HAIC and FOLFOX-HAIC groups. This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of Chongqing University Jiangjin Hospital (KY20240812-001). This study was registered in the Chinese Clinical Trial Registry (ChiCTR2500095127). The

patient's informed consent form before treatment complied with the requirements of the Institutional Review Committee of Chongqing University Jiangjin Hospital.

The inclusion criteria were as follows: (1) age over 18 years; (2) patients who had been pathologically or clinically diagnosed with HCC according to the clinical practice recommendations of the European Association for the Study of the Liver [23]; (3) patients with PVTT who underwent a combination of HAIC and radiotherapy, along with the initial treatment regimen of ICI and TKI; (4) no other malignant tumors; (5) Eastern Cooperative Oncology Group performance 0–1; (6) patients provided informed consent prior to treatment to allow for the retrospective review and reporting of medical records; (7) full follow-up information.

The exclusion criteria were as follows: (1) severe liver dysfunction or other organ failure; (2) distant metastasis, including brain or lung metastasis; (3) severe immune dysfunction diseases such as HIV or organ transplant; (4) incomplete medical information.

2.2 Propensity score matching

Propensity scores for all patients were calculated using logistic regression analysis, taking into account baseline characteristics such as gender, age, body mass index (BMI), viral hepatitis, cirrhosis, HAIC cycle, performance status, and Child–Pugh class. The matching technique employed was the one-to-one nearest-neighbor approach with caliper (0.2) and noreplacement. The variation of standardized deviation, the common value range, and the kernel density map were conducted to detect the matching effect.

2.3 Treatments

2.3.1 HAIC

Using the Seldinger technique to routinely puncture the femoral artery, a 5Fr sheath tube, and catheter were introduced in sequence after successful puncture. Conventional selective catheterization is performed on the abdominal trunk artery and superior mesenteric arteries for angiography to determine the lesion's blood supply and the blood flow through the portal vein. A microcatheter was used to selectively insert the catheter into the hepatic artery. The catheter tip should cover the entire tumor supply area as much as possible and then confirm a satisfactory position by angiography. The catheter position was fixed, the catheter was wrapped around the femoral artery sheath, and 3 M film was used to fix the catheter externally. The catheter was sealed with a heparin cap and heparin saline to prevent thrombosis by blocking the microcatheter. After returning to the ward, hepatic artery infusion chemotherapy was administered through a catheter. The catheter and sheath were removed after completing artery infusion chemotherapy.

The FOLFOX-HAIC regimen artery infusion chemotherapy was as follows: oxaliplatin 85 mg/m^2 from hours 0–3 to day 1, leucovorin 400 mg/m^2 from hours to 3–5, 5-fluorouracil 400 mg/m^2 arterial injected at hour 5, and continuously pumped 5-fluorouracil 2500 mg/m^2 over 46 h. The RALOX-HAIC regimen artery infusion chemotherapy was as follows: oxaliplatin 100 mg/m^2 from hours to 0–3 on day 1 and raltitrexed 3 mg/m^2 from hours 3–6 to on day 1. HAIC therapy was administered every 3 weeks.

2.3.2 Comprehensive systemic therapy

All the patients in this study received comprehensive systemic therapy with TKI and ICI (apatinib combined with camrelizumab or lenvatinib combined with tislelizumab). TKI were administered at a regular daily dosage (8 mg for lenvatinib or 250 mg for apatinib). The dosage of tislelizumab was 200 mg and that of camrelizumab was 200 mg. ICI were administered intravenously once every 3 weeks. TKIs and ICIs dosages should be lowered or discontinued if significant side effects (grade > 3) are noted during treatment.

2.3.3 Radiotherapy

All patients received sequential radiotherapy immediately after initial HAIC treatment. Local radiotherapy using three-dimensional intensity-modulated radiotherapy technology was used for PVTT. The volume of the tumor thrombus, which was created and optimized using three-dimensional reconstruction was used to calculate the gross tumor volume. A

tumor thrombus plus a 10 mm margin in all directions was used to calculate the clinical target volume. The radiotherapy regimen specified a single dose of 1.8 Gy, to be repeated 28 times, resulting in a cumulative treatment dosage of 50.4 Gy.

2.4 Data collection

Clinical information for the entire group was collected from an electronic medical record system. Each patient participated in consistent follow-ups, either through outpatient visits or phone calls. These follow-ups were scheduled to occur monthly following treatment. The deadline for follow-up was March 31, 2025.

The tumor response after 6 weeks from initial treatment was based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [24]. Two radiologists with more than 10 years of experience in liver malignant tumor diagnosis independently compared the follow-up images with baseline images to evaluate the best tumor response to treatment. Objective response rate (ORR) was the percentage of patients achieving a complete response or partial response after starting treatment based on mRECIST criteria. Disease control rate (DCR) was the percentage of patients who experienced a complete response, partial response, or stable disease. Tumor thrombus response was defined as the absence of enhancement in the tumor thrombus or a reduction of at least 30% in the enhanced area of the tumor thrombus during the arterial enhancement phase. Progression-free survival (PFS) was defined as the interval from the start of HAIC until tumor progression or death from any cause. Overall survival (OS) was measured from the time of initial diagnosis to any cause of death. The treatment-related adverse events were classified in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 5.0) [25].

2.5 Statistics analysis

Statistical analysis was performed utilizing SPSS 23.0 and STATA/MP 16.0 Statistics software. For continuous variables, comparisons were made using either the Student's t-test or Mann–Whitney U test. Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Survival rates were determined using the Kaplan–Meier method and subsequently assessed using log-rank tests. Using Cox proportional hazards models for univariate and multivariate analysis to explore the risk factors of OS. A two-tailed P value of less than 0.05 was deemed statistically significant.

3 Results

3.1 Baseline characteristics

Between January 2020 and October 2024, a total of 96 eligible patients with HCC and PVTT were reviewed. After screening based on the inclusion and exclusion criteria, 59 patients for subsequent analysis were finally determined: 27 patients received RALOX-HAIC and 32 patients received FOLFOX-HAIC. There were 51 male patients (86.4%) and 8 female patients (13.6%) in total. There was no statistical difference in gender between the two groups (P = 0.902). Significant difference was found in the age between the two groups (mean age 58.4 vs 51.8, P = 0.029). To balance the baseline feature bias between the two groups, gender, age, BMI, viral hepatitis, cirrhosis, HAIC cycle, performance status, and Child–Pugh class were considered as covariates for propensity scores. After PSM, 21 pairs of patients were evaluated (Fig. 1). There was no statistical difference in age between the two groups after matching (mean age 54.4 vs 56.3, P = 0.513). The equilibrium test and kernel density map revealed that the differential baseline characteristics of the two groups after PSM were balanced and the matching effect was good (Fig. 2). Table 1 provides a detailed comparison of the baseline characteristics between the two groups before and after PSM. There were no significant differences in the other baseline characteristics between the two groups.

3.2 Tumor response

All the patients completed the follow-up as scheduled. The median follow-up duration for the RALOX-HAIC group was 12.7 months, whereas it was 15.4 months for the FOLFOX-HAIC group. There was no statistically significant difference in initial tumor response between the two groups before and after PSM(P = 0.680; 0.314). 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 (Fig. 3). No statistical differences were found in the ORR, DCR, PVTT response, surgical resection rate,

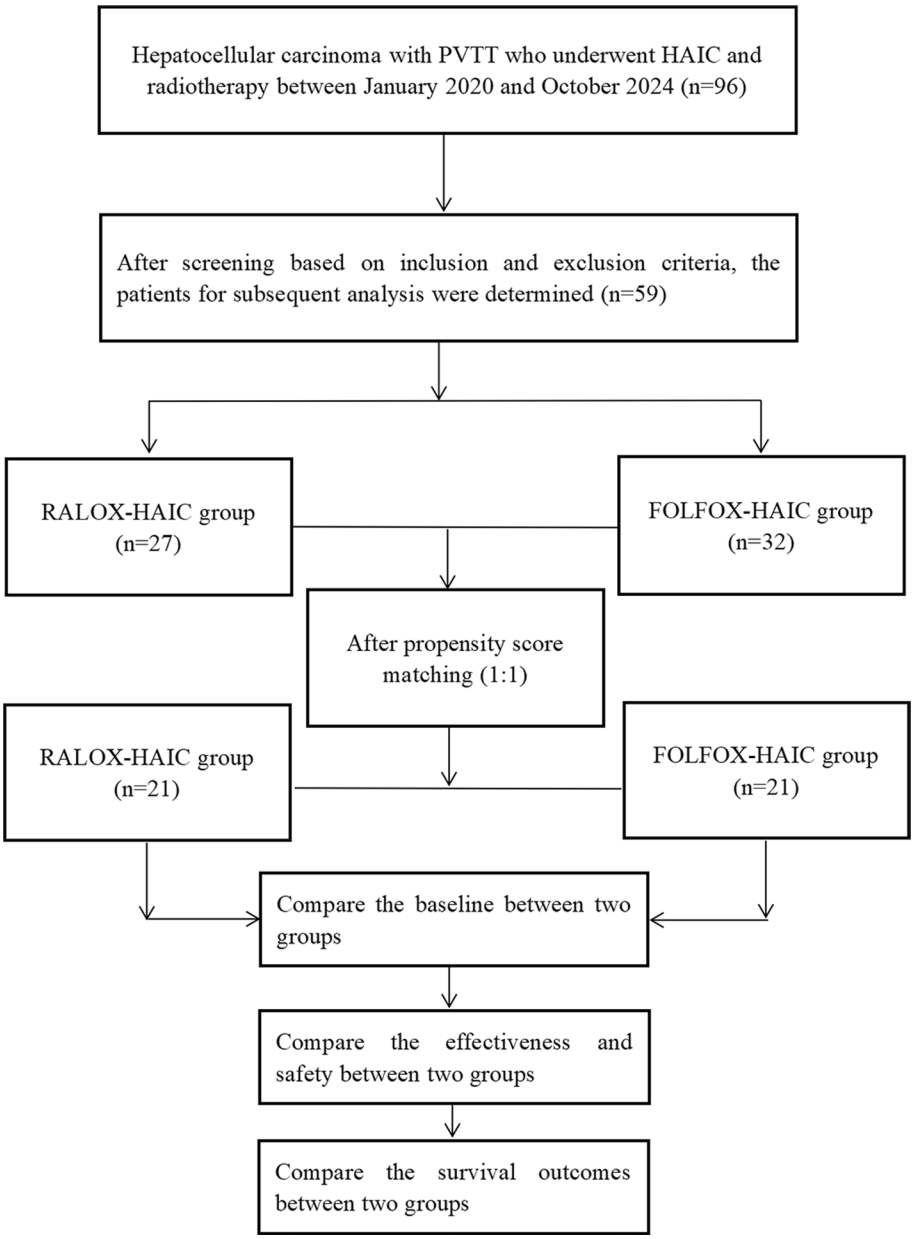

Fig. 1 Research flowchart

metastasis, and mortality between the two groups before and after PSM (Before [ORR: 70.4% vs 65.5%, P = 0.698; DCR: 92.6% vs 96.6%, P = 0.698; PVTT response rate: 81.5% vs 75.0%, P = 0.550; surgical resection rate: 7.4% vs 9.4%, P > 0.999; metastasis: 25.9% vs 37.5%, P = 0.343; mortality: 51.8% vs 62.5%, P = 0.410]; After [ORR: 71.4% vs 671.4%, P = 1.000; DCR: 90.5% vs 100.0%, P = 0.469; PVTT response rate: 80.9% vs 71.4%, P = 0.469; surgical resection rate: 9.5% vs 14.3%, P > 0.999; metastasis: 23.8% vs 33.3%, P = 0.495; mortality: 47.6% vs 66.7%, P = 0.212]). Table 2 details the tumor effectiveness in the two groups of patients before and after PSM.

3.3 Treatment-related adverse events

None of the patients interrupted treatment or died within 30 days due to treatment-related adverse events. The most common treatment-related adverse events of these patients were abdominal pain (31/59, 52.5%), gastrointestinal symptoms (19/59, 32.2%), fever (14/59, 23.7%), myelosuppression (12/59, 20.3%), and gastrointestinal hemorrhage (6/59, 10.2%). The incidence of severe adverse events was 6.8% (4/59). Compared with the FOLFOX-HAIC group, the incidences of abdominal pain and fever was lower in the RALOX-HAIC group (abdominal pain: 37.0% vs 65.6%,

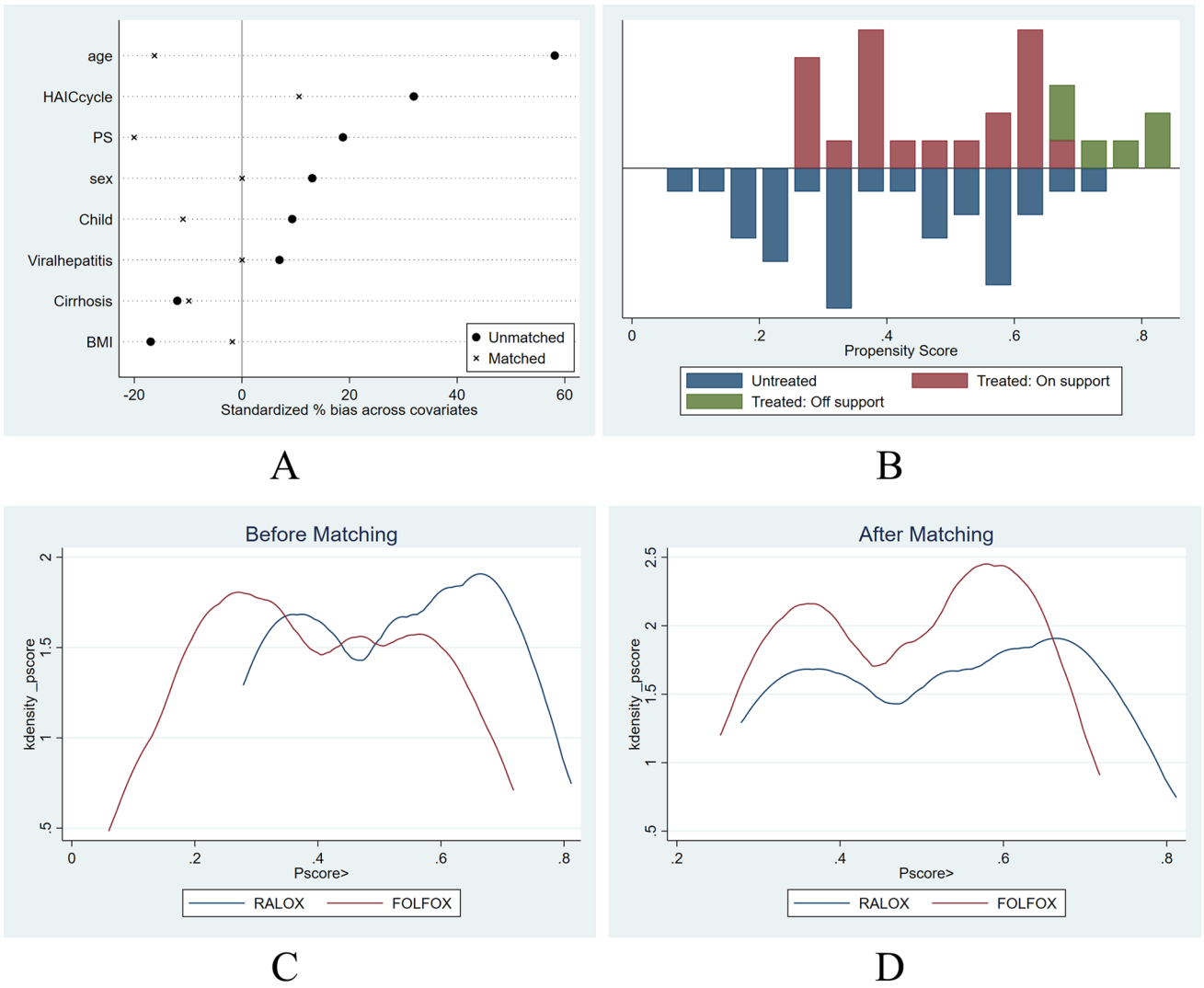

Fig. 2 The results of propensity score matching; **A** The standardized deviation of difference features decreased significantly after matching; **B** After matching, the two groups have a preferable common value range; **C** The kernel density map before propensity score matching; **D** The kernel density map after propensity score matching. HAIC, hepatic artery infusion chemotherapy; PS, performance status; BMI, body mass index

P = 0.028; fever: 14.8% vs 31.3%, P = 0.029). These differences still had statistical significance after PSM (abdominal pain: 38.1% vs 76.2%, P = 0.013; fever: 9.5% vs 42.8%, P = 0.014). Before and after PSM, no significant differences in other adverse events rate and severe adverse events rate between the two groups were observed. Table 2 details the treatment-related adverse events in the two groups of patients before and after PSM.

3.4 Survival analysis

Before PSM, the median PFS for the RALOX-HAIC group was 15.3 months, whereas it was 13.5 months for the FOLFOX-HAIC group (hazard ratio [HR] = 0.876; 95%CI 0.448–1.715; P = 0.699; Fig. 4A). The median OS for the RALOX-HAIC group was 15.5 months, whereas it was 14.2 months for the FOLFOX-HAIC group (HR = 1.138; 95%CI 0.569–2.276; P = 0.715; Fig. 4B). After PSM, the median PFS for the RALOX-HAIC group was 12.7 months, whereas it was 12.5 months for the FOLFOX-HAIC group (HR = 0.792; 95%CI 0.359–1.748; P = 0.564; Fig. 4C). The median OS for the RALOX-HAIC group was 15.5 months, whereas it was 14.6 months for the FOLFOX-HAIC group (HR = 0.998; 95%CI 0.438–2.274; P = 0.995; Fig. 4D).

Table 1 The baseline characteristics of hepatocellular carcinoma with PVTT underwent HAIC and radiotherapy

Variables	Before PSM			After PSM		
	RALOX (n = 27)	FOLFOX (n = 32)	P	RALOX (n = 21)	FOLFOX (n = 21)	P
Gender, n (%)			0.902			1.000
Male	24 (88.9)	27 (84.4)		19 (90.5)	19 (90.5)	
Female	3 (11.1)	5 (15.6)		2 (9.5)	2 (9.5)	
Age, Mean ± SD	58.4 ± 12.2	51.8 ± 10.6	0.029*	54.4 ± 10.3	56.3 ± 7.8	0.513
BMI(kg/m^2), Mean ± SD	21.6 ± 2.4	22.1 ± 2.8	0.521	21.2 ± 1.9	21.2 ± 1.6	0.933
HAIC cycle, Mean ± SD	3.6 ± 1.5	3.1 ± 1.2	0.223	3.4 ± 1.4	3.2 ± 1.2	0.730
Systemic therapy plan			0.852			0.758
Apatinib and Camrelizumab	15 (55.6)	17 (53.1)		10 (47.6)	11 (52.4)	
Lenvatinib and Tislelizumab	12 (44.4)	15 (46.9)		11 (52.4)	10 (47.6)	
Viral hepatitis, n (%)	25 (92.6)	29 (90.6)	> 0.999	20 (95.2)	20 (95.2)	1.000
Cirrhosis, n (%)	17 (63.0)	22 (68.8)	0.640	15 (71.4)	16 (76.2)	0.726
ECOG score			0.465			0.525
0	17 (63.9)	23 (71.9)		14 (66.7)	12 (57.1)	
1	10 (26.1)	9 (28.1)		7 (33.3)	9 (42.9)	
Cheng's classification, n (%)			0.641			0.334
I/II	16 (59.3)	21 (65.6)		12 (57.1)	15 (71.4)	
III/IV	11 (40.7)	11 (34.4)		9 (42.9)	6 (28.6)	
Child–Pugh class, n (%)			0.716			0.726
A (5–6)	20 (74.1)	25 (78.1)		16 (76.2)	15 (71.4)	
B (7–9)	7 (25.9)	7 (21.9)		5 (23.8)	6 (28.6)	
ALBI, n (%)			0.663			0.528
1 (≤ − 2.60)	4 (14.8)	5 (15.6)		3 (14.3)	2 (9.5)	
2 (− 2.60 ~ − 1.39)	22 (81.5)	24 (75.0)		17 (80.9)	16 (76.2)	
3 (≥ − 1.39)	1 (3.7)	3 (9.4)		1 (4.8)	3 (14.3)	
Tumor diameter(cm), Mean ± SD	9.8 ± 3.9	9.4 ± 3.3	0.639	10.1 ± 4.1	8.9 ± 3.4	0.281
Tumor > 5 cm, n (%)	24 (88.9)	28 (87.5)	> 0.999	18 (85.7)	17 (80.9)	> 0.999
Number of tumors > 3, n (%)	14 (51.9)	22 (68.8)	0.185	10 (47.6)	14 (66.7)	0.212
Tumor capsule, n (%)	14 (51.9)	14 (43.8)	0.535	9 (42.9)	9 (42.9)	1.000
AFP > 400, n (%)	14 (51.9)	17 (53.1)	0.922	12 (57.1)	11 (52.4)	0.757
TB(umol/L), Median (Q1, Q3)	14.8 (11.2, 19.1)	17.9 (13.7, 22.9)	0.173	15.4 (13.2, 19.1)	18.9 (15.5, 25.8)	0.237
Pre-albumin(mg/L), Mean ± SD	146.2 ± 56.1	171.4 ± 72.3	0.137	145.5 ± 56.8	151.8 ± 71.9	0.753
Albumin(g/L), Mean ± SD	36.1 ± 4.8	37.9 ± 5.3	0.187	36.4 ± 4.9	36.6 ± 5.2	0.916
ALT(U/L), Median (Q1, Q3)	51.0 (30.0, 84.0)	46.5 (39.0, 61.5)	0.778	58.0 (34.0, 84.0)	47.0 (40.0, 55.0)	0.285
AST(U/L), Median (Q1, Q3)	71.0 (42.0, 155.0)	61.0 (54.0, 94.0)	0.964	83.0 (52.0, 155.0)	68 (56.0, 97.0)	0.571

PVTT, Portal vein tumor thrombus; HAIC, hepatic artery infusion chemotherapy; PSM, Propensity score matching; BMI, Body Mass Index; ALBI, Albumin-bilirubin; TB, Total bilirubin; ALT, Alanine asninotrasferase; AST, Aspartic transaminase; AFP, Alpha-fetoprotein; SD, Standard deviations.*The difference is statistically significant

RALOX:Oxaliplatin plus Rituximab; FOLFOX: Oxaliplatin + Leucovorin + Fluorouracil

3.5 Univariate and multivariate analysis of OS

The result of the univariate Cox proportional hazards models analysis revealed that performance status score and prealbumin < 170 mg/L were the risk factors of OS for HCC patients with PVTT who initially underwent HAIC combined radiotherapy, TKI, and ICI. The factors with P < 0.1 in univariate analysis were included into multivariate Cox proportional hazards models analysis. The result showed that prealbumin < 170 mg/L (HR = 2.234; 95%CI 1.051–4.751; P = 0.037) was the independent risk factor for OS. The comprehensive findings were presented in Table 3.

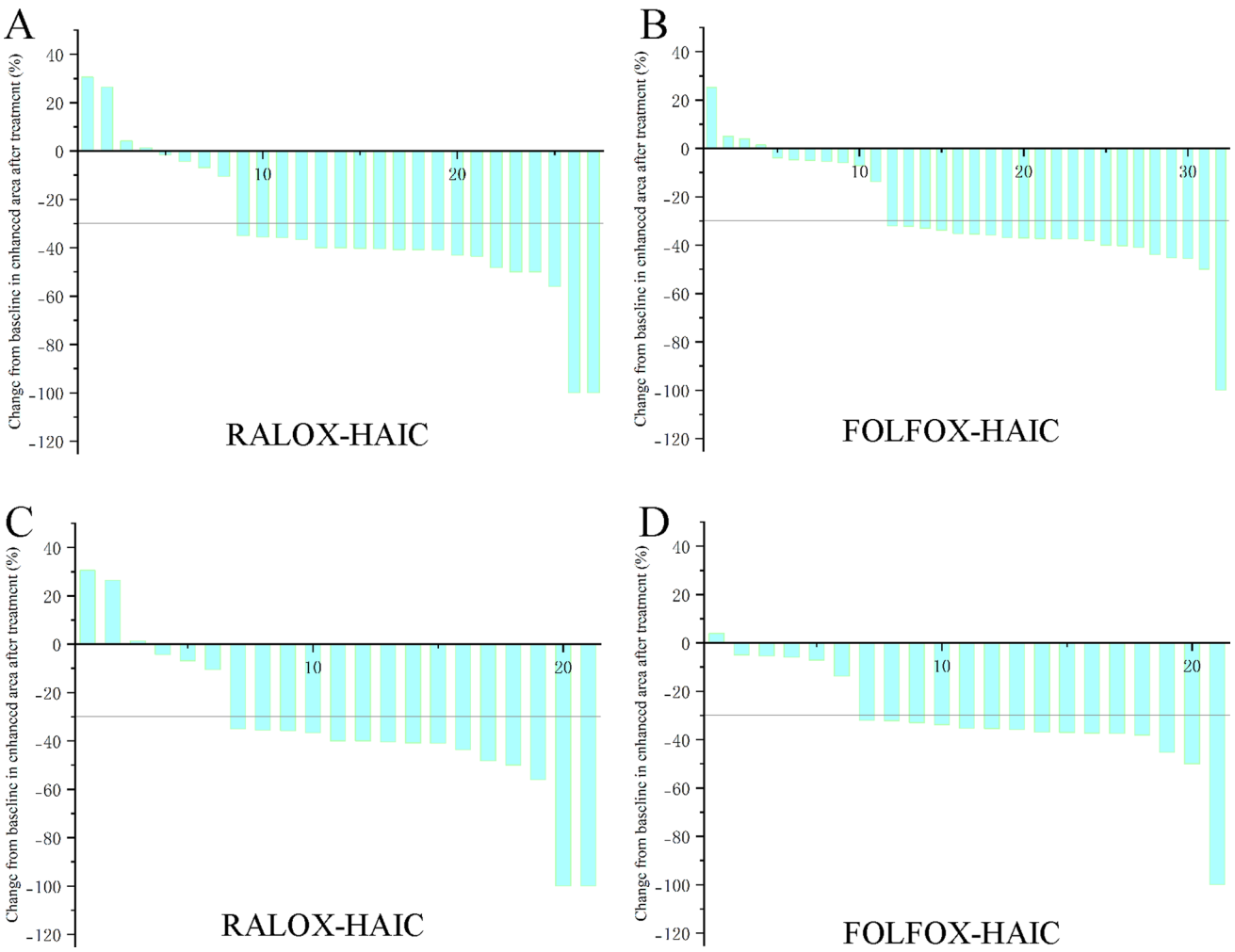

Fig. 3 Waterfall plots for the best percentage change in tumor enhancement area after treatment for six weeks based on the modified Response Evaluation Criteria in Solid Tumors; **A** Tumor changes in the RALOX-HAIC group before propensity score matching; **B** Tumor changes in the FOLFOX-HAIC group before propensity score matching; **C** Tumor changes in the RALOX-HAIC group after propensity score matching; **D** Tumor changes in the FOLFOX-HAIC group after propensity score matching

4 Discussion

The treatment of HCC patients with PVTT has always been a major challenge in the comprehensive treatment of liver cancer because of its poor curative effect. A series of studies have shown that comprehensive treatment, mainly based on HAIC, such as TKI and ICI, can improve the therapeutic effectiveness of HCC with PVTT [26, 27]. Our previous research revealed that HAIC combined with radiotherapy, TKI, and ICI can improve OS and PFS for HCC with PVTT [15]. However, there are some difficulties in clinical practice. Long-term bed rest and immobilization can increase patient discomfort and the psychological burden. This may have affected patient compliance. Therefore, we aimed to shorten the bed rest time to ensure therapeutic efficacy. Previous studies have indicated that HAIC with oxaliplatin plus raltitrexed has shown promising results for patients with advanced HCC ineligible for or failing transarterial chemoembolization [28]. Compared to the FOLFOX regimen, RALOX-HAIC demonstrated better progression-free survival and overall survival, particularly in patients with type II PVTT [29]. However, there is a lack of relevant research on RALOX-HAIC combined with radiotherapy, TKI, and ICI for HCC patients with PVTT. Therefore, this retrospective cohort study aimed to evaluate its safety and effectiveness in providing additional treatment experiences.

Our study indicated that the RALOX-HAIC group patients and the FOLFOX-HAIC group patients had similar PFS, OS, and tumor effectiveness, such as tumor response, ORR, DCR, PVTT response, surgical resection rate, metastasis, and

Table 2 Comparison of effectiveness and safety between the RALOX-HAIC group and the FOLFOX-HAIC group

Variables	Before PSM			After PSM		
	RALOX (n = 27)	FOLFOX (n = 32)	P	RALOX (n = 21)	FOLFOX (n = 21)	P
Initial tumor response			0.680			0.314
Complete response (CR)	2 (7.4)	1 (3.1)		2 (9.5)	1 (4.8)	
Partial response (PR)	17 (63.0)	20 (62.5)		13 (61.9)	14 (66.7)	
Stable disease (SD)	6 (22.2)	10 (31.3)		4 (19.1)	6 (28.5)	
Progressive disease (PD)	2 (7.4)	1 (3.1)		2 (9.5)	0	
ORR, n (%)	19 (70.4)	21 (65.6)	0.698	15 (71.4)	15 (71.4)	1.000
DCR, n (%)	25 (92.6)	31 (96.9)	0.880	19 (90.5)	21 (100)	0.469
PVTT response, n (%)	22 (81.5)	24 (75.0)	0.550	17 (80.9)	15 (71.4)	0.469
Surgical resection, n (%)	2 (7.4)	3 (9.4)	> 0.999	2 (9.5)	3 (14.3)	> 0.999
Metastasis, n(%)	7 (25.9)	12 (37.5)	0.343	5 (23.8)	7 (33.3)	0.495
Deadline death, n(%)	14 (51.8)	20 (62.5)	0.410	10 (47.6)	14 (66.7)	0.212
Treatment-related adverse events						
Fever, n(%)	4 (14.8)	10 (31.3)	0.029*	2 (9.5)	9 (42.8)	0.014*
Abdominal pain, n (%)	10 (37.0)	21 (65.6)	0.028*	8 (38.1)	16 (76.2)	0.013*
Gastrointestinal symptoms, n (%)	9 (33.3)	10 (31.3)	0.865	7 (33.3)	5 (23.8)	0.495
Elevated transaminase, n (%)	3 (11.1)	2 (6.3)	0.842	3 (14.3)	2 (9.5)	> 0.999
Hypoalbuminemia, n (%)	2 (7.4)	1 (3.1)	0.880	2 (9.5)	1 (4.8)	> 0.999
Ascites, n (%)	2 (7.4)	2 (6.3)	> 0.999	2 (9.5)	2 (9.5)	1.000
Gastrointestinal hemorrhage, n (%)	2 (7.4)	4 (12.5)	0.832	2 (9.5)	3 (14.3)	> 0.999
Myelosuppression, n (%)	5 (18.5)	7 (21.9)	0.750	4 (19.1)	3 (14.3)	> 0.999
Severe adverse events, n (%)	1 (3.7)	3 (9.3)	0.731	1 (4.8)	1 (4.8)	1.000

PVTT, Portal vein tumor thrombus; HAIC, hepatic artery infusion chemotherapy; PSM, Propensity score matching; ORR, Objective response rate; DCR, Disease control rate.*The difference is statistically significant

RALOX:Oxaliplatin plus Rituximab; FOLFOX: Oxaliplatin + Leucovorin + Fluorouracil

mortality. However, the RALOX-HAIC group patients had lower incidences of treatment-related abdominal pain and fever. The results of propensity score matching were also consistent. Meanwhile, the prealbumin < 170 mg/L before comprehensive therapy was an independent risk factor for OS. Therefore, we should pay attention to the patient's prealbumin levels before comprehensive therapy and correct low levels to improve overall survival. The highlights of this study include the following points: (1) propensity score matching was conducted to enhance the evidence strength of the results; (2) the RALOX-HAIC group patients and the FOLFOX-HAIC group patients had similar tumor effectiveness, but the RALOX-HAIC group patients had lower incidences of treatment-related abdominal pain and fever; (3) the prealbumin < 170 mg/L before comprehensive therapy was an independent risk factor for OS.

Some aspects of this study need to be emphasized. Firstly, we should discuss the issues of gender and age. As is well known, liver cancer is more common in men. This may be the reason why the proportion of males in our study is significantly higher than that of females. And, there is no difference in the choice of treatment between males and females. To ensure the reliability of the results, we used gender as a balancing factor for propensity score matching, but also found that gender is not a risk factor for OS. As for age difference, the selection of FOLFOX or RALOX was entirely based on the patient's personal choice. Therefore, elderly patients tend to prefer treatment plans with shorter arterial perfusion times, which results in older age in the RALOX-HAIC group. However, the results after propensity score matching used age as a balancing factor are also consistent, and age is not a risk factor for OS either. Therefore, we can assume that the differences of gender and age will not affect our results. Secondly, we need to discuss the issue of follow-up time. Owing to updates in concepts and technology, the proportion of patients receiving RALOX-HAIC treatment gradually increased between 2022 and 2024 in our center. This results in a shorter median follow-up time for most RALOX-HAIC patients, which does not fully reflect the survival situation. Based on the current research stage, the effectiveness of RALOX-HAIC is not inferior to that of FOLFOX-HAIC. Then, we will conduct a prospective study to further investigate the effects of RALOX-HAIC and FOLFOX-HAIC on survival. Finally, we should also discuss the differences in FOLFOX-HAIC regimens. The current mainstream therapeutic regimen of

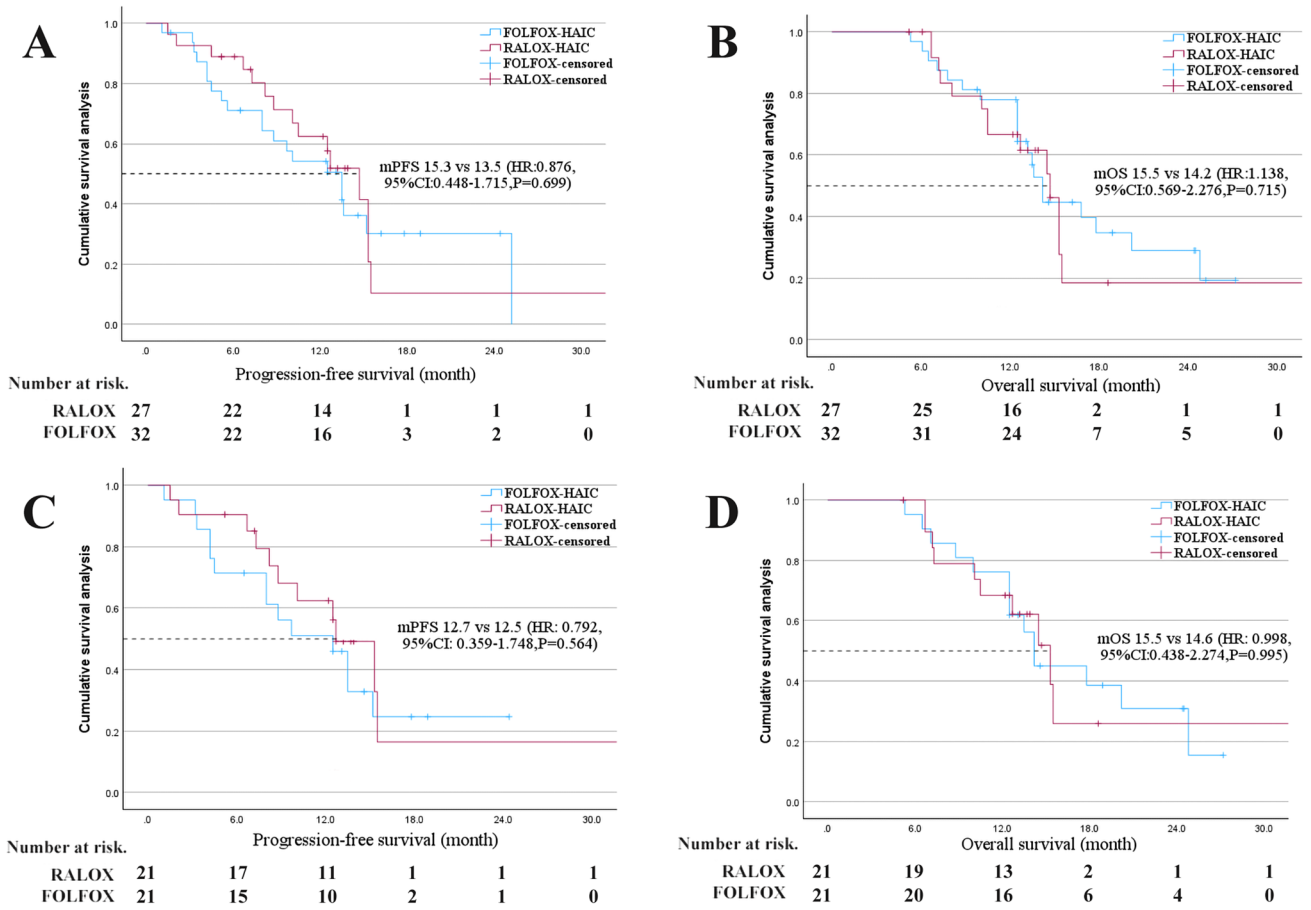

Fig. 4 Kaplan–Meier curves of survival outcome between two groups; **A** Comparison of progression free survival between the two groups before propensity score matching; **B** Comparison of overall survival between the two groups before propensity score matching; **C** Comparison of progression free survival between the two groups after propensity score matching; **D** Comparison of overall survival between the two groups after propensity score matching. HAIC, hepatic artery infusion chemotherapy; HR, hazard ratio; mPFS, median progression free survival; mOS, median overall survival

HAIC treatment is oxaliplatin plus leucovorin and 5-fuorouracil over 46 h [16]. Many researchers are trying to adjust the arterial perfusion regimen to increase comfort and safety, such as replacement with raltitrexed, or 5-fluorouracil shortened to 23 h. In this study, we assume that the combination of long half-life drugs and radiotherapy can improve overall efficacy. Therefore, we compared RALOX-HAIC with the mainstream FOLFOX-HAIC. It is worth comparing the one-day FOLFOX-HAIC with RALOX-HAIC and the two-days FOLFOX-HAIC in the future research to explore the differences in therapeutic effects.

There are also some limitations to the current research that need to be pointed out. Due to its retrospective design and the development of new technologies, despite of propensity score matching, the study had a limited sample size and brief follow-up duration. Consequently, randomized controlled trials involving larger groups and extended follow-up periods are needed to confirm these results. In addition, the specific arterial perfusion regimen of RALOX-HAIC is unclear because there have been few related studies. This study selected the most common regimen, which may not necessarily be the best. Therefore, further investigation is required to determine the optimal perfusion protocol for RALOX-HAIC.

5 Conclusion

Our study reveals that the RALOX-HAIC combined radiotherapy, TKI, and ICI may provide similar survival advantages with fewer treatment-related abdominal pain and fever compared to FOLFOX-HAIC for HCC patients with PVTT. The prealbumin < 170 mg/L before therapy is an independent risk factor for OS.

Table 3 Univariate and multivariate Cox analyses to evaluate the predictors for overall survival

	Univariate analysis				Multivariate regression analysis			
	Hazard ratio (HR)	95%CI		P value	Hazard ratio (HR)	95%CI		P value
		Lower	Upper			Lower	Upper	
Gender	1.519	0.533	4.327	0.434				
Age	0.979	0.953	1.005	0.119				
BMI	0.929	0.786	1.099	0.393				
HAIC cycle	0.931	0.705	1.230	0.615				
RALOX-HAIC	1.138	0.569	2.276	0.715				
Systemic therapy	0.980	0.499	1.925	0.953				
Viral hepatitis	1.744	0.416	7.315	0.447				
Cirrhosis	1.155	0.548	2.437	0.705				
ECOG score	2.132	1.085	4.187	0.028*	1.643	0.804	3.357	0.173
PVTT classification	1.324	0.672	2.610	0.417				
Child–Pugh class	1.857	0.885	3.895	0.101				
ALBI	1.989	0.842	4.702	0.117				
Tumor diameter	0.963	0.876	1.058	0.428				
Tumor > 5 cm	0.712	0.274	1.856	0.488				
Tumor number ≤ 3	1.314	0.653	2.645	0.444				
Tumor capsule	0.946	0.477	1.873	0.873				
TB > 17.1umol/L	0.654	0.320	1.336	0.244				
Albumin < 35 g/L	1.507	0.743	3.058	0.256				
Prealbumin < 170 mg/L	2.621	1.282	5.359	0.008*	2.234	1.051	4.751	0.037*
ALT > 40 U/L	0.939	0.456	1.933	0.864				
AST > 40 U/L	0.871	0.359	2.113	0.760				

BMI: Body Mass Index; PVTT: Portal vein tumor thrombus; ALBI: Albumin-bilirubin; TB: Total bilirubin; ALT: Alanine asninotrasferase; AST: Aspartic transaminase; AFP: Alpha-fetoprotein; HR: Hazard Ratio

*The p-value is statistically significant

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Author contributions All authors contributed to the study conception and design. Material preparation was performed by Hua-guo Feng and Guo-hua Dai. Data collection and analysis were performed by Shuang-quan Liu, Jiu-ling Zheng, and Yan-han Liu. The first draft of the manuscript was written by Hao-yang Tan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration

Ethics approval and consent for participation This study adhered to the guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of Chongqing University Jiangjin Hospital (KY20240812-001). This study was registered in the Chinese Clinical Trial Registry (ChiCTR2500095127). The patient's informed consent form before treatment complied with the requirements of the Institutional Review Committee of Chongqing University Jiangjin Hospital. Informed consent was obtained from all individual participants included in the study.

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

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