BMC Cancer

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Efficacy and safety of postoperative adjuvant HAIC with FOLFOX combining PD-1 inhibitors in HCC patients with microvascular invasion: a propensity score matching analysis

Yuxin Liang[1,2†], Deyuan Zhong[1,2†], Jin Shang[1], Hongtao Yan[1], Yuhao Su[1], Yahui Chen[1], Qinyan Yang[1,3*] and Xiaolun Huang[1,3*]

Abstract

Purpose To evaluate the efficacy and safety of postoperative adjuvant hepatic arterial infusion chemotherapy (PA-HAIC) plus programmed death-1 (PD-1) inhibitors versus PA-HAIC alone for hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI).

Methods This retrospective study included HCC patients with MVI who were treated with either PA-HAIC or PA-HAIC plus PD-1 inhibitors between February 2021 and February 2024. The differences in baseline characteristics, disease-free survival (DFS), and overall survival (OS) were compared between the two groups before and after propensity score-matching (PSM). The treatment-related adverse events (TRAEs) were compared among the two groups after PSM. Cox regression analysis was utilized to determine factors affecting DFS and OS.

Results A total of 102 patients were included in the study: 65 in the PA-HAIC group and 37 in the PA-HAIC plus PD-1 group. PSM analysis generated 32 matched pairs of patients in the two groups. The HCC patients in the PA-HAIC plus PD-1 group experienced significantly better DFS compared to those in the PA-HAIC group alone (HR: 0.412; $P=0.031$). However, there was no significant difference in OS between the two groups ($P=0.124$). Multivariate analysis identified the treatment option (PA-HAIC vs. PA-HAIC + PD-1) as an independent predictive factor for DFS of the patients. Furthermore, the results indicated no statistically significant difference in the incidence of TRAEs between the two groups ($P<0.05$).

Conclusion In comparison with PA-HAIC alone, PA-HAIC combined with PD-1 inhibitors could improve the DFS benefits with acceptable safety profiles in HCC patients with MVI.

Keywords Hepatocellular carcinoma, Microvascular invasion, PA-HAIC, PD-1 inhibitors, Combined therapy

†Yuxin Liang and Deyuan Zhong contributed equally to this work.

*Correspondence:
Qinyan Yang
lizayangyang@hotmail.com
Xiaolun Huang
huangxiaolun@med.uestc.edu.cn
[1]Department of Liver Transplantation Center and HBP Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Center, School of Medicine, Sichuan Cancer Hospital & Institute, University of Electronic Science and Technology of China, Chengdu, China
[2]Department of Hepatobiliary-Pancreatic Surgery, Cell Transplantation Center, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China
[3]Present address: Department of Liver Transplantation Center and HBP Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Introduction

Hepatocellular carcinoma (HCC), which accounts for 75–85% of primary liver cancer cases, was one of the most prevalent and lethal malignancies worldwide [1]. Despite advances in treatment strategies, surgical resection remains the first-line curative option for HCC patients [2]. However, the postoperative recurrence rate of HCC was 70-80%, leading to poor efficacy and prognosis [3]. Therefore, several promising postoperative adjuvant therapies are being explored to reduce the risk of recurrence and mortality, including the IMbrave050 study with positive results [4]. Nevertheless, the overall outcomes of various postoperative adjuvant therapies remain variable, making the improvement of postoperative prognosis for HCC patients a major challenge [5].

There are several high-risk factors for postoperative recurrence of HCC, including multiple tumors, microvascular or macrovascular invasion, and lymph node metastasis [4]. Multiple studies have identified microvascular invasion (MVI) as a significant risk factor for early recurrence and overall survival (OS) of HCC patients after curative hepatectomy [6–8]. Recently, two pioneering studies demonstrated that postoperative adjuvant hepatic arterial infusion chemotherapy (PA-HAIC) with 5-fluorouracil and oxaliplatin (FOLFOX) significantly improved the survival benefits in HCC patients with MVI [9, 10]. Additionally, adjuvant anti-programmed death-1 (PD-1) therapy has also been shown to effectively improve the postoperative prognosis of HCC patients at high risk of recurrence [11, 12]. However, whether PA-HAIC with FOLFOX combining PD-1 inhibitors presents favorable survival outcomes in HCC patients with MVI remains unknown.

Therefore, the purpose of the current study was to evaluate and compare the efficacy and safety of PA-HAIC combined with PD-1 inhibitors versus PA-HAIC alone in the treatment of HCC patients with MVI.

Materials and methods

Patient cohort and study design

The present study enrolled the clinicopathological data of HCC patients who underwent PA-HAIC with FOLFOX + PD-1 Inhibitors or PA-HAIC With FOLFOX alone at Sichuan Cancer Hospital and Sichuan Provincial People's Hospital between February 2021 and February 2024. The inclusion criteria were as follows: (1) histologically confirmation of HCC with MVI; (2) Eastern Cooperative Oncology Group performance score of 0 or 1; (3) no previous or concomitant anticancer therapy; (3) R0 surgical resection of tumor with curative intent; (4) HAIC with FOLFOX + PD-1 Inhibitors or HAIC alone as the only postoperative adjuvant therapy. The exclusion criteria were as follows: (1) having history of non-HCC malignancies; (2) preoperative presence of HCC recurrence, macrovascular invasion, or distant metastasis; (3) allergy to related drugs or intolerance to HAIC; (4) died within 30 days after surgery; (5) incomplete data. Finally, 102 patients were recruited into our study. The flowchart of the study design is presented in Fig. 1.

This retrospective study was approved by the Human Ethics Committee of Sichuan Cancer Hospital. All procedures were performed in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants in the study.

Follow up

The follow-up was conducted every 4–8 weeks during the first postoperative year, and every 3 months thereafter if no recurrence or metastasis was detected. Each follow-up included laboratory tests and either computed tomography (CT) or magnetic resonance imaging (MRI). The primary outcome was disease-free survival (DFS), defined as the duration from surgery to the occurrence of recurrence, metastasis, or death, whichever occurred first. The secondary outcome was OS, defined as the interval from surgery to death due to all causes. Patients who had not experienced recurrence, metastasis, or death by the end of the follow-up (May 2024) were censored as alive and event-free.

Clinicopathological data collection

All clinicopathological characteristics associated with postoperative prognosis were collected within 7 days prior to surgery. These characteristics included age, sex, body mass index (BMI), laboratory test results, tumor features, and clinical stages. The laboratory tests primarily assessed serum markers, liver function, coagulation status, and hepatitis B virus markers. Tumor features encompassed histopathological type, presence of cirrhosis, tumor number, the diameter of the largest nodule, and MVI. MVI was defined as the presence of a tumor within a vascular space lined by endothelium, detectable only through microscopy [13].

Treatment

Four to six weeks after surgery, all patients received either PA-HAIC with FOLFOX + PD-1 inhibitors or PA-HAIC with FOLFOX alone. The HAIC procedure was conducted according to previously reported protocols [9]. Firstly, percutaneous femoral artery puncture and catheterization were performed on the patients. The hepatic artery was then intubated to the predetermined position using superior mesenteric arteriography and hepatic arteriography, and patients with indwelling catheters were transferred to the ward. In the ward, the catheter was connected to an infusion pump to deliver the following chemotherapeutic agents continuously: oxaliplatin (85 mg/m^2) from 0 to 3 h on day 1; leucovorin (400 mg/

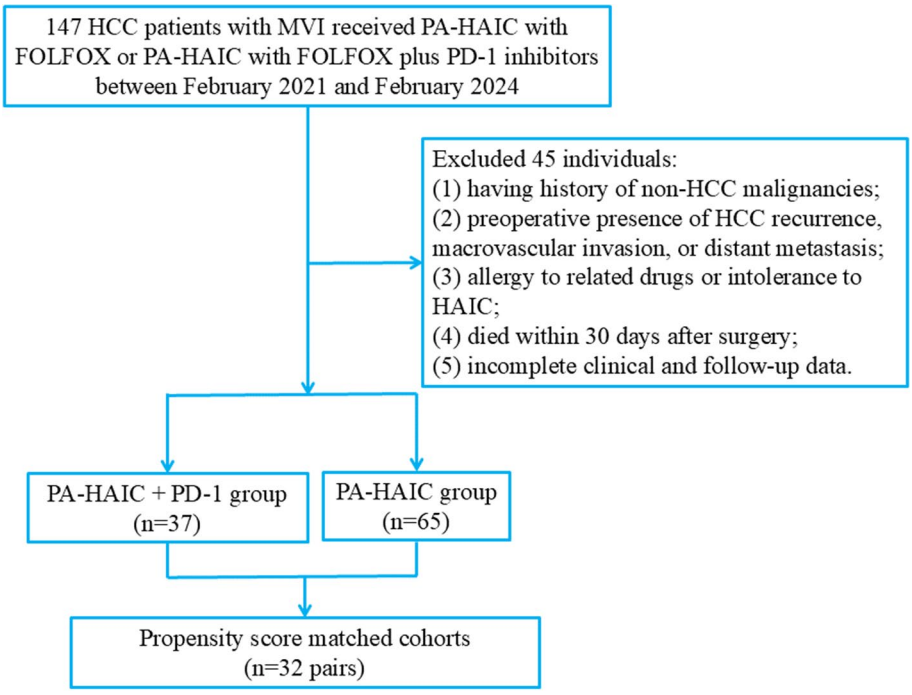

Fig. 1 The flowchart of patient enrollment. Abbreviations HCC, hepatocellular carcinoma; MVI, microvascular invasion; PA-HAIC, postoperative adjuvant hepatic arterial infusion chemotherapy; FOLFOX, 5-fluorouracil and oxaliplatin; PD-1, programmed cell death protein 1

m^2) from 3 to 4.5 h on day 1; fluorouracil (400 mg/m^2) from 4.5 to 6.5 h on day 1; and fluorouracil (2,400 mg/m^2) over 46 h from days 1 to 3. Patients remained bedridden during chemotherapy. After completing chemotherapy, the catheter was pulled out, and patients were discharged following complete hemostasis at the puncture site. Patients typically received two cycles of HAIC, with a 4-week interval between cycles. Efficacy was monitored periodically through clinical assessments and imaging to determine whether adjustments to the treatment regimen were necessary. The regimen was discontinued due to unacceptable toxicity, patient decision, or disease progression.

PD-1 inhibitors (Sintilimab) were administered intravenously at a dose of 200 mg every three weeks. The dosage was reduced or discontinued based on the severity of toxic side effects, following the manufacturer's guidelines.

Statistical analysis

Continuous variables were presented as medians with interquartile ranges (Q1–Q3) or as mean ± standard deviation, while categorical variables were presented as frequency (%). Between the two groups, categorical variables were compared by the Chi-square test or Fisher's exact test, and continuous variables were compared by the Student's t test or Mann-Whitney U test. The propensity score model included the following variables: age, gender, etiology of HCC, cirrhosis, and Child-Pugh grade. To address potential confounder imbalances between the two groups, propensity score matching (PSM) analysis was conducted using the 1:1 nearest-neighbor method with a caliper width of 0.05. Survival curves for DFS and OS were generated by the Kaplan–Meier method, and the differences were compared using the log rank test. Univariate and multivariate Cox regression analyses were conducted to determine independent prognostic factors. All factors that were statistically significant in the univariate analysis ($P < 0.1$) were included in the multivariate analysis to identify independent predictors of DFS and OS. Statistical analyses were carried out using SPSS software version 22.0. A two-sided P-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 102 HCC patients with MVI were enrolled in this study, including 65 patients in the PA-HAIC group and 37 patients in the PA-HAIC + PD-1 group. The baseline clinicopathological characteristics before and after PSM were listed in Table 1. Before PSM, there was no significant difference in baseline characteristics between the two groups ($P > 0.05$). Following PSM, the matched cohort of 32 patients in each group demonstrated well-balanced baseline characteristics.

Survival analysis

In the present study, the median follow-up time was 18 months (IQR 10.0-26.3 months). At the end of follow-up,

Table 1 Baseline characteristics of the HCC patients before and after PSM

Characteristics	Before PSM			After PSM		
	PA-HAIC (*n* = 65)	PA-HAIC + PD-1 (*n* = 37)	*P* value	PA-HAIC (*n* = 32)	PA-HAIC + PD-1 (*n* = 32)	*P* value
Age, years	57 ± 11	55 ± 10	0.497	56 ± 11	56 ± 10	0.868
Gender	0.402					1.000
Male	54 (83.1%)	33 (89.2%)		29 (90.6%)	28 (87.5%)	
Female	11 (16.9%)	4 (10.8%)		3 (9.4%)	4 (12.5%)	
BMI, kg/m^2	22.3 (20.9–25.4)	21.6 (20.2–23.4)	0.073	23.2 ± 3.3	22.0 ± 1.7	0.075
Etiology of HCC			0.322			0.756
HBV	47 (72.3%)	30 (81.1%)		25 (78.1%)	26 (81.3%)	
Others	18 (27.7%)	7 (18.9%)		7 (21.9%)	6 (18.8%)	
BCLC stage			0.419			0.539
0/A	25 (38.5%)	16 (43.2%)		11 (34.4%)	13 (40.6%)	
B	20 (30.8%)	14 (37.8%)		10 (31.3%)	12 (37.5%)	
C	20 (30.8%)	7 (18.9%)		11 (34.4%)	7 (21.9%)	
Child-Pugh class			0.732			1.000
A	49 (75.4%)	29 (78.4%)		27 (84.4%)	27 (84.4%)	
B	16 (24.6%)	8 (21.6%)		5 (15.6%)	5 (15.6%)	
ALT, U/L	30 (23–49)	33 (20–53)	0.947	31 (25–49)	30 (17–44)	0.424
ALB, g/L	39.1 (34.9–41.6)	38.2 (35.8–40.5)	0.360	39.1 (37.2, 41.7)	38.6 (35.9–40.9)	0.417
Bilirubin, μmol/L	17.4 (13.6–25.0)	16.3 (11.5–21.5)	0.231	18 (13.5–25.0)	17.1 (11.4–21.6)	0.365
Leukocyte count, 10^9/L	5.09 (3.91–6.70)	5.03 (3.78–6.10)	0.473	4.88 (4.29–6.74)	5.07 (3.86–6.05)	0.409
Neutrophil count, 10^9/L	3.30 (2.51–4.27)	2.94 (2.26–3.77)	0.358	3.07 (2.61–4.81)	2.94 (2.35–3.83)	0.167
Platelet count, 10^9/L	114 (80–189)	146 (86–171)	0.821	114 (85–166)	148 (86–169)	0.809
AFP, ng/mL	32 (8.39–352)	84.66 (2.73-642.21)	0.573	45.04 (7.89-490.49)	103.11 (2.71-695.71)	0.562
Tumor size (cm)	6.5 (4.0–9.0)	6.0 (3.7–9.5)	0.931	6.5 (4.4–9.3)	6.0 (3.5–9.4)	0.767
Tumor number			0.223			0.616
Single	38 (58.5%)	17 (45.9%)		16 (50.0%)	14 (43.8%)	
Multiple	27 (41.5%)	20 (54.1%)		16 (50.0%)	18 (56.3%)	
Histopathological type			0.609			0.768
Poorly differentiation	17 (26.2%)	8 (21.6%)		8 (25.0%)	7 (21.9%)	
Medium-high differentiation	48 (73.8%)	29 (78.4%)		24 (75.0%)	25 (78.1%)	
Cirrhosis			0.942			1.000
No	18 (27.7%)	10 (27.0%)		7 (21.9%)	7 (21.9%)	
Yes	47 (72.3%)	27 (73.0%)		25 (78.1%)	25 (78.1%)	
ALBI grade			0.935			0.446
1	24 (36.9%)	15 (40.5%)		11 (34.4%)	14 (43.8%)	
2	39 (60.0%)	21 (56.8%)		21 (65.6%)	17 (53.1%)	
3	2 (3.1%)	1 (2.7%)		0 (%)	1 (3.1%)	
hsCRP, mg/L	2.56 (0.94–8.54)	1.81 (0.58–5.11)	0.170	2.04 (0.61–5.47)	1.65 (0.57–4.90)	0.676

Abbreviations HCC, hepatocellular carcinoma; PSM, propensity score matching; PA-HAIC, postoperative adjuvant hepatic arterial infusion chemotherapy; PD-1, programmed cell death protein 1; BMI, body mass index; HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; ALT, alanine transaminase; ALB, albumin; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; hsCRP, high-sensitivity C-reactive protein

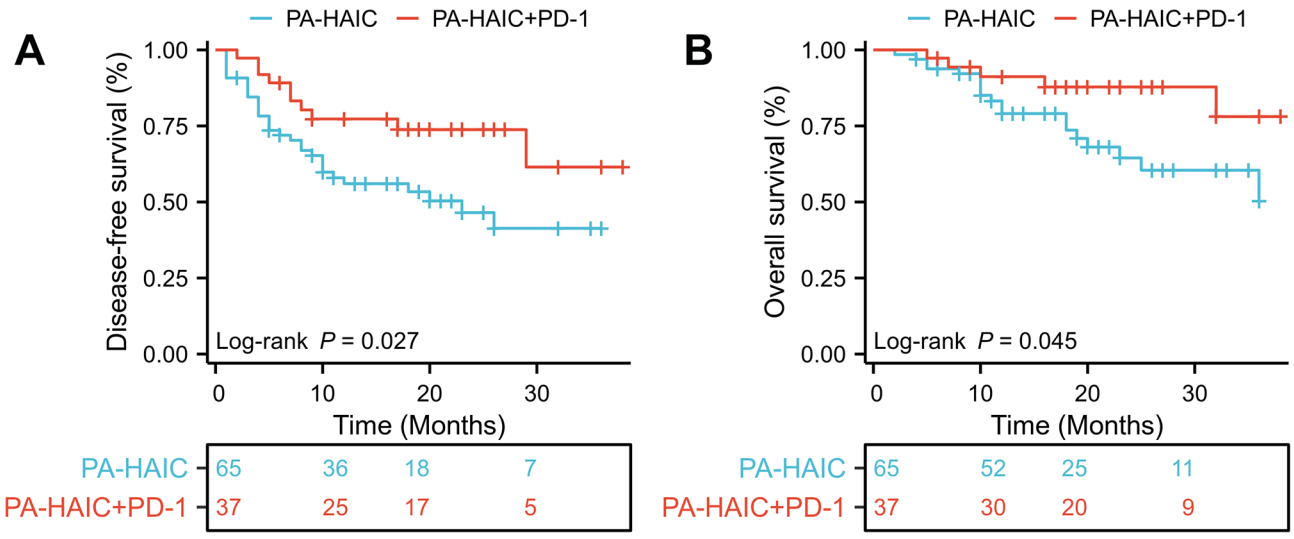

Fig. 2 Kaplan–Meier survival curves of disease-free survival (**A**) and overall survival (**B**) for the HCC patients in the two groups before PSM. Abbreviations HCC, hepatocellular carcinoma; PSM, propensity score matching; HAIC, hepatic arterial infusion chemotherapy; PD-1, programmed cell death protein 1

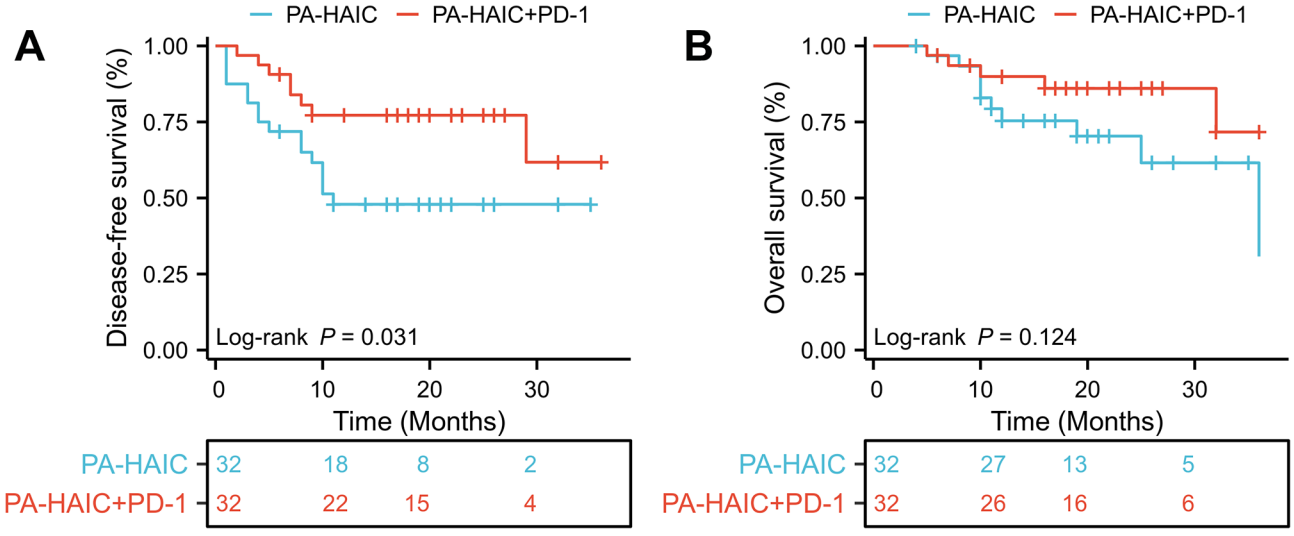

Fig. 3 Kaplan–Meier survival curves of disease-free survival (**A**) and overall survival (**B**) for the HCC patients in the two groups after PSM. Abbreviations HCC, hepatocellular carcinoma; PSM, propensity score matching; HAIC, hepatic arterial infusion chemotherapy; PD-1, programmed cell death protein 1

10 (27.0%) patients presented cancer progression, and 5 (13.5%) patients died in the PA-HAIC + PD-1 group. Moreover, 31 (47.7%) patients presented cancer progression, and 19 (29.2%) patients died in the PA-HAIC group. Before PSM, patients in the PA-HAIC + PD-1 group were associated with significantly better DFS and OS compared with those in the PA-HAIC group (HR: 0.463; 95% CI: 0.249–0.863; $P = 0.027$; Fig. 2A; HR: 0.384; 95% CI: 0.170–0.867; $P = 0.045$; Fig. 2B). After PSM, patients in the PA-HAIC + PD-1 group were also associated with significantly better DFS compared with those in the PA-HAIC group (HR: 0.412; 95% CI: 0.184–0.921; $P = 0.031$; Fig. 3A). However, there was no significant difference in OS between the two groups ($P = 0.124$; Fig. 3B).

Analysis of independent prognostic factors

In the matched cohort, all indicators were divided into categorical variables and analyzed using univariate and multivariate Cox regression analyses (Table 2). From the univariate analysis, we found that age (< 60 years vs. ≥60 years, $P = 0.058$), tumor number (single vs. multiple, $P = 0.031$), and treatment option (PA-HAIC group vs. PA-HAIC + PD-1 group, $P = 0.036$) were significantly associated with DFS in the HCC patients ($P < 0.1$). Additionally, bilirubin levels (< 20 μmol/L vs. ≥20μmol/L, $P = 0.041$), tumor number (single vs. multiple, $P = 0.014$), and tumor size (< 5 cm vs. ≥5 cm, $P = 0.079$) were significantly associated with OS in the HCC patients ($P < 0.1$). Multivariate analysis further indicated that tumor number (HR: 2.648;

Table 2 Univariate and multivariate Cox regression analyses of the predictors for disease-free survival and overall survival of the HCC patients after PSM

Characteristics	DFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years (< 60 vs. ≥60)	0.400 (0.155–1.032)	0.058	0.436 (0.168–1.129)	0.087	1.206 (0.433–3.363)	0.720		
Bilirubin, μmol/L (< 20 vs. ≥20)	1.093 (0.485–2.468)	0.830			0.261 (0.072–0.947)	0.041	0.328 (0.080–1.348)	0.122
Tumor number (Single vs. Multiple)	2.655 (1.095–6.435)	0.031	2.648 (1.079–6.499)	**0.034**	4.926 (1.380–17.582)	0.014	6.337 (1.576–25.485)	**0.009**
ALT, U/L (< 35 vs. ≥35)	1.726 (0.774–3.849)	0.183			2.296 (0.824–6.395)	0.112		
Histopathological type (Poorly vs. Medium-high)	0.932 (0.369–2.351)	0.881			0.983 (0.308–3.136)	0.977		
Cirrhosis (No vs. Yes)	1.234 (0.459–3.319)	0.676			0.863 (0.273–2.729)	0.802		
AFP, ng/mL (< 400 vs. ≥400)	0.977 (0.405–2.358)	0.958			1.711 (0.608–4.816)	0.309		
Tumor size, cm (< 5 vs. ≥5)	1.584 (0.627–4.002)	0.331			3.815 (0.858–16.969)	0.079	3.809 (0.795–18.237)	0.094
ALB, g/L (≤ 35 vs. >35)	0.753 (0.257–2.208)	0.605			1.078 (0.239–4.868)	0.922		
Treatment (PA-HAIC vs. PA-HAIC + PD-1)	0.401 (0.171–0.940)	0.036	0.357 (0.151–0.845)	**0.019**	0.439 (0.149–1.289)	0.134		

Table 3 Treatment-related adverse events of the HCC patients after PSM

Events, *n* (%)	PA-HAIC (*n* = 32)			PA-HAIC + PD-1 (*n* = 32)			*P* value		
	Any Grade	Grade 1/2	Grade 3/4	Any Grade	Grade 1/2	Grade 3/4	Any Grade	Grade 1/2	Grade 3/4
Any TRAE	27	27	6	29	25	8	0.705	0.522	0.545
Hematologic toxic effects									
Leukopenia	5	4	1	8	6	2	0.351	0.491	> 0.999
Thrombocytopenia	3	3	0	3	2	1	> 0.999	> 0.999	> 0.999
Hepatic function									
Increased ALT	5	4	1	8	6	1	0.351	0.491	> 0.999
Increased AST	4	4	0	4	2	2	> 0.999	0.668	0.472
Hyperbilirubinemia	0	0	0	3	3	0	0.237	0.237	> 0.999
Nonhematologic toxic effects									
Nausea	7	5	2	11	9	2	0.266	0.226	> 0.999
Fatigue	6	4	2	7	6	1	0.756	0.491	> 0.999
Fever	3	3	0	4	4	0	> 0.999	> 0.999	> 0.999
Hypertension	5	5	0	3	3	0	0.705	0.705	> 0.999
Pain	10	10	0	9	8	1	0.784	0.578	> 0.999
Diarrhea	3	3	0	4	4	0	> 0.999	> 0.999	> 0.999
Hypothyroidism	0	0	0	3	3	0	0.237	0.237	> 0.999
Gastrointestinal hemorrhage	1	1	0	2	2	0	> 0.999	> 0.999	> 0.999
RCCEP	0	0	0	2	2	0	0.472	0.472	> 0.999

95% CI: 1.079–6.499; $P = 0.034$) and treatment option (HR: 0.357; 95% CI: 0.151–0.845; $P = 0.019$) were independent predictive factors for DFS, while tumor number (HR: 6.337; 95% CI: 1.576–25.485; $P = 0.030$) was identified as an independent predictive factor for OS.

Safety

To evaluate the safety differences between the two groups after PSM, treatment-related adverse events (TRAEs) were presented in Table 3. The incidence of TRAEs was comparable between the PA-HAIC group and PA-HAIC + PD-1 group (any grade: 84.4% vs. 90.6%, $P = 0.705$). In the PA-HAIC + PD-1 group, 3 patients

(9.4%) experienced grade 1/2 hypothyroidism, while 2 patients (6.3%) experienced grade 1/2 gastrointestinal hemorrhage and reactive cutaneous capillary endothelial proliferation. None of these events were observed in the PA-HAIC group. There was no statistically significant difference in these events between the two groups ($P < 0.05$). Importantly, no treatment-related mortality or TRAEs above grade 4 were reported in either group. All TRAEs were resolved following symptomatic treatment or discontinuation of therapy.

Discussion

To date, there is no universally accepted postoperative adjuvant therapy for HCC patients with MVI [10]. In the present study, we found that the HCC patients in the PA-HAIC + PD-1 group experienced significantly better DFS compared to those in the PA-HAIC group alone (HR: 0.412; $P = 0.031$; Fig. 3A). However, there was no significant difference in OS between the two groups ($P = 0.124$; Fig. 3B). Multivariate analysis identified the treatment option (PA-HAIC group vs. PA-HAIC + PD-1 group; HR: 0.357; $P = 0.019$) as an independent predictive factor for DFS in HCC patients with MVI. Furthermore, the results indicated no statistically significant difference in the incidence of TRAEs between the two groups ($P < 0.05$), demonstrating acceptable safety profiles of both treatments.

The main reasons for early postoperative recurrence of HCC are the intrahepatic spread and micrometastasis of tumor cells, both of which are high-risk outcomes associated with MVI in HCC patients [14, 15]. Previous studies have reported that postoperative adjuvant transarterial chemoembolization (PA-TACE) yielded favorable survival outcomes in HCC patients with MVI [16, 17], while complications caused by embolization have limited its clinical applicability [10]. Recently, PA-HAIC with FOLFOX has shown survival benefits and manageable safety concerns in HCC patients with MVI, with a median DFS as 20.3 months [10]. Moreover, multiple studies have demonstrated that the combination of HAIC and PD-1 inhibitors produces promising results and acceptable safety profiles in patients with intermediate and advanced HCC [18–20]. In the current study, following PSM, the HCC patients with MVI who received PA-HAIC combining PD-1 inhibitors experienced significantly better DFS compared to those receiving PA-HAIC alone (HR: 0.412; $P = 0.031$; Fig. 3A). Moreover, the treatment option (PA-HAIC group vs. PA-HAIC + PD-1 group; HR: 0.357; $P = 0.019$) was identified as an independent predictor of DFS in HCC patients with MVI. These findings suggested that PA-HAIC plus PD-1 inhibitors might be an effective treatment strategy for postoperative HCC patients with MVI.

Recent studies have investigated the combination of chemotherapy and immune checkpoint inhibitors, demonstrating enhanced antitumor effects [21–23]. The promising outcomes of the combination therapy may be attributed to several factors. First, the continuous infusion of chemotherapy drugs directly into the tumor induces tumor cell death and eliminates micrometastasis in the liver and bloodstream [10, 24]. Second, FOLFOX drugs infused by HAIC could induce tumor apoptosis through DNA damage and cytoplasmic effects. Additionally, it triggers immunogenic cell death of tumor cells, leading to the release of tumor antigens. These processes enhance the anti-tumor immune response, thereby improving the efficacy of anti-PD-1 therapy [25]. Furthermore, PD-1 inhibitors enhance antitumor activity by targeting immune checkpoints and activating cytotoxic T lymphocyte function [26, 27]. In summary, the combination of PA-HAIC and anti-PD-1 therapy may exert synergistic antitumor effects, contributing to favorable survival outcomes.

In the present study, tumor number (Single vs. Multiple) was identified as an independent risk factor for DFS and OS, which was consistent with previous studies [28–30]. For HCC patients with multiple tumors, continuous infusion of chemotherapy drugs into the hepatic artery, rather than embolization, could ensure sufficient intratumoral drug concentrations, enhance anti-tumor activity, and ultimately contribute to a good prognosis of these patients.

In our findings, the combination of PA-HAIC with PD-1 inhibitors was generally well-tolerated and consistent with previous studies [10, 18, 20]. All TRAEs were no higher than grade 4 and were comparable between the PA-HAIC group and PA-HAIC plus PD-1 group, with no new or unexpected TRAEs observed. After symptomatic treatment or medication discontinuation, all TRAEs were resolved. These results demonstrated that PA-HAIC plus PD-1 inhibitors did not increase the risk of TRAEs compared to PA-HAIC alone, indicating an acceptable safety profiles.

There were some limitations in this study. First, the selection of treatment options in this retrospective study was influenced by the preferences of both physicians and patients, introducing selection bias into the study population. Therefore, we adopted the PSM model to mitigate the impact of confounding factors on the results. Second, this was a small sample study with a short follow-up time, which limited the generalizability of the findings. Further large scale, randomized controlled clinical trials are needed to validate these results. In addition, before applying PSM, patients in the PA-HAIC + PD-1 group exhibited significantly better OS compared to those in the PA-HAIC group (HR: 0.384; $P = 0.045$; Fig. 2B). However, after PSM, there was no significant difference in OS between the two groups ($P = 0.124$; Fig. 3B). We believe that a longer follow-up period and larger sample sizes

might reveal the survival benefits of PA-HAIC plus PD-1 inhibitors.

Conclusion

In summary, in comparison with PA-HAIC alone, PA-HAIC plus PD-1 inhibitors could improve the DFS benefits with acceptable safety profiles in HCC patients with MVI.

Author contributions

Y.L. and D.Z. were responsible for study conceptualization, data analysis, drafting and revision of the manuscript. Q.Y. and X.H. were responsible for study conceptualization, validation, and revision of the manuscript. J.S., H.Y., Y.S., and Y.C. were responsible for validation and revision of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by Sichuan Province Science and Technology Support Program (No. 2021YFH0187, No. 2024YFHZ0358).

Data availability

The data supporting the findings of our study are available from the corresponding author under reasonable requirements.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Human Ethics Committee of Sichuan Cancer Hospital. All procedures were performed in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants in the study.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Received: 29 September 2024 / Accepted: 21 February 2025
Published online: 07 March 2025

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