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ORIGINAL RESEARCH

Prognostic Value of Alpha-Fetoprotein in Unresectable Hepatocellular Carcinoma Treated with Hepatic Artery Infusion Chemotherapy Combined with Lenvatinib and Camrelizumab

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Purpose: This study aimed to assess the prognostic significance of alpha-fetoprotein (AFP) response in patients with unresectable hepatocellular carcinoma (u-HCC) who underwent hepatic artery infusion chemotherapy (HAIC) combined with lenvatinib and camrelizumab.

Methods: A retrospective review was conducted on patients with u-HCC receiving treatment with HAIC combined with lenvatinib and camrelizumab. Early AFP response was defined as a >20% decrease in AFP within 4 weeks, and AFP response as a >75% decrease in AFP within 8 weeks. The correlation between early AFP response, AFP response, therapeutic response, overall survival (OS), and progression-free survival (PFS) was investigated.

Results: The study included 63 patients. AFP responders exhibited superior objective response rates compared to AFP non-responders, as determined by RECIST v1.1 or mRECIST criteria (45.5 vs. 18.2%, p=0.014, or 81.8 vs. 48.5%, p=0.013). Furthermore, early AFP responders demonstrated prolonged OS (not reached vs. 8.0 months, p<0.001) and PFS (13.3 vs. 3.0 months, p= 0.018) relative to early AFP non-responders. Similarly, AFP responders exhibited improved OS (not reached vs. 9.0 months, p<0.001) and PFS (19.3 vs. 5.1 months, p=0.002) compared to AFP non-responders. Multivariate analysis results indicated that both early AFP response and AFP response independently predicted OS [hazard ratio (HR) 2.963, 95% confidence interval (CI) 1.333–6.585, p=0.008, and HR 6.182, 95% CI 1.780–21.466, p=0.004] and PFS (HR 2.186, 95% CI 1.107–4.318, p=0.024, and HR 3.078, 95% CI 1.407–6.730, p=0.005), serving as significant prognostic values.

Conclusion: Early AFP response and AFP response serve as predictive biomarkers for the effectiveness of HAIC combined with lenvatinib and camrelizumab in patients with u-HCC.

Keywords: unresectable hepatocellular carcinoma, alpha-fetoprotein, hepatic arterial infusion chemotherapy, lenvatinib, camrelizumab

Introduction

Hepatocellular carcinoma (HCC) was the most prevalent primary liver tumor and the third leading cause of cancer-related mortality globally. According to the World Health Organization, liver cancer will cause 1.3 million deaths by 2040.[1,2] However, due to the absence of noticeable symptoms in the early stages of HCC, most diagnosed patients do not

have widespread access to surgical intervention, despite the favorable 70% 5-year survival rate following resection.[3,4] As a result, approximately 50–60% of the patients eventually undergo systemic therapy.[5] Lenvatinib, a tyrosine kinase inhibitor, has gained popularity as a treatment option for unresectable HCC (u-HCC) due to its proven non-inferiority to sorafenib and increasing utilization.[6] The advent of immune checkpoint inhibitors has revolutionized the management of u-HCC. One such inhibitor, camrelizumab, a programmed cell death protein-1 inhibitor, has demonstrated improved survival outcomes in Chinese u-HCC patients.[7] However, the efficacy of monotherapy was limited. The publication of promising outcomes from the IMBrave150 trial has established the combination therapy, incorporating drugs with diverse mechanisms of action, as the standard treatment for patients with u-HCC.[8] Moreover, hepatic arterial infusion chemotherapy (HAIC) has shown a high response rate and improved survival in u-HCC, with the combination of HAIC and sorafenib demonstrating enhanced survival benefits compared to sorafenib alone.[9–12] Hence, the combination of HAIC, lenvatinib, and camrelizumab holds the potential as an effective treatment option for u-HCC.[13–16]

Alpha-fetoprotein (AFP) is the most widely utilized and crucial biomarker for HCC. Elevated AFP levels often indicate more aggressive tumors and are associated with a poorer prognosis, and baseline AFP serum concentrations ≥400 ng/mL frequently suggest poor survival.[17] Numerous studies have investigated the correlation between AFP response and prognosis during treatment.[18–25] Zhu et al demonstrated that patients with HCC receiving atezolizumab plus bevacizumab, who achieved a reduction of ≥75% in AFP levels from baseline within 6 weeks, had improved overall survival (OS) and progression-free survival (PFS) compared to those with a reduction of <75%.[21] A meta-analysis comprising 12 clinical studies, involving 464 patients receiving systemic therapy and 510 patients receiving local therapy for HCC, revealed a reduced risk of death among patients who demonstrated an AFP response.[26] However, the relationship between AFP response and the prognosis of patients with u-HCC undergoing HAIC combined with lenvatinib and camrelizumab has not been explored.

This study aimed to evaluate the relationship among baseline AFP levels, AFP response during treatment, and prognosis in patients with u-HCC who underwent HAIC combined with lenvatinib and camrelizumab.

Materials and Methods
Patients
A retrospective analysis was conducted on patients with u-HCC who received treatment with HAIC combined with lenvatinib and camrelizumab at the First Affiliated Hospital, Jiangxi Medical College, Nanchang University, between October 2020 and April 2022. The study included patients who met the following criteria: 1) age ≥18 years, and according to the EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma,[27] patients with a diagnosis of HCC who, after comprehensive Discussion by the multidisciplinary treatment, were determined to be inoperable or unlikely to derive clinical benefit from surgical resection; 2) Child-Pugh liver function score was A or B7; 3) received at least 1 HAIC treatment, received lenvatinib for ≥3 months, and completed ≥3 cycles of camrelizumab; 4) The patient's AFP information is complete at baseline and 4 weeks post-treatment.; 5) The patient is naively treated for HCC and is not diagnosed with any malignancy other than HCC.

The research received approval from the Hospital Ethics Committee and adhered to the ethical principles of the Declaration of Helsinki.

HAIC
The HAIC procedure was conducted following the previously described protocol.[13,16] A senior interventionalist performed the procedure using the Seldinger technique, inserting a catheter through the right femoral artery under digital subtraction angiography guidance to precisely locate the tumor and identify blood supply vessels. A 2.7F catheter was then positioned at the main blood supply artery of the tumor. The therapeutic regimen consisted of FOLFOX, including oxaliplatin at 85 mg/m² via continuous infusion over 2 hours, leucovorin at 400 mg/m² via continuous infusion over 2 hours, and 5-fluorouracil at 2400 mg/m² via continuous infusion for 46 hours. Drug doses were adjusted based on liver function reserve and chemotherapy tolerance. The catheter was removed after completing HAIC and reinserted for subsequent cycles. HAIC sessions occurred every 3 weeks for up to 6 cycles.

Lenvatinib and Camrelizumab

Patients with u-HCC initiated treatment with lenvatinib and camrelizumab within three days before or after their initial HAIC session. Those with a bodyweight <60 kg received an oral daily dose of 8 mg of lenvatinib, while those weighing ≥60 kg were prescribed a daily dose of 12 mg. Camrelizumab was administered intravenously at a dose of 200 mg every three weeks. Drug dose adjustments or discontinuation were implemented in cases of disease progression or intolerable toxicity.

AFP

AFP levels were measured prior to initiating treatment and subsequently monitored every four weeks after starting the treatment. The rate of change of AFP was calculated using the following formula: Rate of change =(Test value − Baseline value)/Baseline value. In accordance with previous studies, we defined early AFP response as a decrease in AFP levels of more than 20% within 4 weeks and AFP response as a decrease of more than 75% within 8 weeks.[21,25]

Evaluation and Data Collection

All patients underwent enhanced CT/MRI after three weeks of HAIC treatment or every 6–8 weeks following the completion of HAIC treatment. Efficacy was evaluated by two senior imaging specialists using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)[28] and the Modified Response Evaluation Criteria in Solid Tumors (mRECIST).[29] Overall Survival (OS) was defined as the time from treatment initiation to death from any cause, and Progression-Free Survival (PFS) was the time from treatment initiation to radiologic progression of disease or death. The Disease Control Rate (DCR) was calculated by summing the rates of Complete Response (CR), Partial Response (PR), and Stable Disease (SD). The Objective Response Rate (ORR) was calculated by summing the rates of CR and PR. Patients' liver function was assessed using the Child-Pugh classification.[30,31] The Japanese Liver Cancer Study Group criteria were applied for staging portal vein tumor thrombosis (PVTT) and hepatic vein tumor thrombosis (HVTT) based on the tumor thrombus location.[32] The Barcelona Clinical Liver Cancer (BCLC) staging system determined the stage of HCC.[33]

Statistical Analysis

Continuous variables were assessed for normality and presented as mean ± standard deviation (for normally distributed data) or as the median and interquartile range (IQR). Categorical variables were compared using the χ^2 test or Fisher's exact test. Kaplan–Meier survival analysis determined median survival time and 95% confidence intervals, with Log-Rank tests used for comparing survival curves. The COX proportional hazards model analyzed variables, with those having $p < 0.1$ in the univariate analysis considered for inclusion in the multivariate analysis. A significance level of $p < 0.05$ was applied. Statistical analyses were conducted using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (http://www.r-project.org/).

Results

A total of 88 patients with u-HCC underwent treatment HAIC combined with lenvatinib and camrelizumab. Among them, 14 patients received the non-FOLFOX regimen for HAIC, and 11 patients had elevated AFP levels above the upper limit of detection at baseline, 4 weeks, or 8 weeks after treatment initiation, leading to the unavailability of accurate values. Additionally, one patient was lost to follow-up, resulting in the inclusion of a total of 63 patients in this study. Table 1 provides comprehensive details on the patients' baseline characteristics. The cohort consisted of 52 males and 11 females, with a median age of 53 (48–63) years. Seven patients had a Child-Pugh score of 7, and one had an ECOG PS of 1. The majority of patients (57/63) had hepatitis B-related HCC. The median maximum tumor diameter was 9.3 (6.2–12.5) cm, with 42 patients having four or more intrahepatic nodules. Furthermore, 32 patients exhibited combined macrovascular invasion, including 4, 15, and 11 patients with Vp2, Vp3, and Vp4, respectively, and two each with Vv2 and Vv3. Notably, two patients had both HVTT and PVTT. Patients with BCLC stage A, B, and C comprised 4, 18, and 41 patients, respectively. The baseline AFP

Table 1 Demographic Characteristics of the Patients

Characteristics	ALL (n = 63)	>20% AFP Decrease Within 4 Weeks			>75% AFP Decrease Within 8 Weeks		
		Yes (n = 46)	No (n = 17)	p-value	Yes (n = 22)	No (n = 33)	p-value
Sex (male/female), n	52/11	36/10	16/1	0.272	16/6	30/3	0.157
Age, median [IQR], (years)	53 (48–63)	54 (49–64)	50 (43–55)	0.026	54 (48–64)	52 (46–61)	0.440
Child-Pugh classification (A5/A6/B7), n	33/23/7	25/16/5	8/7/2	0.872	9/12/1	20/9/4	0.110
ECOG PS (0/1), n	62/1	45/1	17/0	1.000	21/1	33/0	0.400
AFP at baseline, median [IQR], (ng/mL)	316.0 (20.7–3621.0)	461.2 (21.3–13,625)	131.7 (8.09–1452.3)	0.233	1186.5 (112.3–8569.3)	154.3 (11.0–3946.5)	0.280
Aetiology of HCC (Hepatitis B/non-B, non-C), n	57/6	44/2	13/4	0.069	19/3	30/3	0.930
Tumor Number (1/2/3/≥4), n	16/4/1/42	13/4/1/28	3/0/0/14	0.465	7/1/0/14	8/2/1/22	0.936
Maximum diameter of tumor, median [IQR], (cm)	9.3 (6.2–12.5)	9.0 (6.2–11.5)	10.8 (8.6–14.8)	0.072	8.2 (6.4–12.6)	10.0 (7.9–12.5)	0.455
PVTT (NO/Vp2/Vp3/Vp4), n	33/4/15/11	26/3/11/6	7/1/4/5	0.510	11/3/4/4	17/0/9/7	0.110
HVTT (NO/Vv2/Vv3), n	59/2/2	43/1/2	16/1/0	0.420	20/0/2	31/2/0	0.057
Macrovascular invasion (yes/no), n	32/31	21/25	11/6	0.179	12/10	17/16	0.825
Extrahepatic Spread (present/absent), n	13/50	9/37	4/13	1.000	3/19	10/23	0.154
BCLC Stage (A/B/C), n	4/18/41	4/15/27	0/3/14	0.100	2/7/13	1/7/25	0.372
Hemoglobin, median [IQR], (g/L)	129 (110–142)	129 (116–142)	121 (104–143)	0.693	129 (116–137)	129 (106–146)	0.679
Neutrophils, median [IQR], (*10^9/L)	3.17 (2.29–4.90)	3.09 (2.17–4.48)	4.34 (3.09–7.38)	0.006	3.22 (2.16–4.85)	3.36 (2.49–5.75)	0.542
Lymphocytes, median [IQR], (*10^9/L)	1.10 (0.85–1.50)	1.09 (0.72–1.69)	1.23 (0.88–1.49)	0.547	1.07 (0.81–1.54)	1.21 (0.86–1.60)	0.902
Platelet count, median [IQR], (*10^9/L)	162 (102–236)	146 (102–226)	229 (123–260)	0.063	141 (101–265)	207 (108–243)	0.498
Albumin, median [IQR], (g/L)	35.5 (33.2–39.1)	36.2 (34.1–40.4)	35.4 (32.6–37.4)	0.346	35.1 (33.7–38.0)	36.6 (33.1–40.1)	0.642
Total bilirubin, median [IQR], (μmol/L)	17.3 (10.7–26.1)	16.3 (10.6–22.4)	19.3 (11.4–25.4)	0.857	17.6 (10.7–28.1)	16.3 (10.5–22.1)	0.624
AFP within 4 weeks, median [IQR], (ng/mL)	81.2 (8.9–1745.0)	79.9 (9.9–1745.0)	170.0 (7.5–1520.3)	0.586	149.4 (22.3–776.4)	39.9 (6.5–2729.0)	0.885
AFP within 8 weeks, median [IQR], (ng/mL) *	32.4 (4.5–934.0)	32.4 (4.5–926.7)	68.7 (4.1–2594.0)	0.993	9.7 (3.7–388.9)	116.2 (7.4–8107.0)	0.055
Follow-up duration, median [IQR], (months)	15.4 (14.3–16.5)	15.4 (14.2–16.6)	16.8 (12.9–20.7)	0.785	16.1 (14.7–17.5)	13.5 (12.1–14.9)	0.314
HAIC Cycle, median (range)	3 (1–5)	3 (1–4)	3 (1–5)	–	3 (1–4)	3 (1–5)	–
Cycles of Camrelizumab therapy, median (range)	6 (3–29)	7 (3–29)	7 (3–14)	–	8 (3–23)	6 (3–29)	–

Note: *8 patients missing.
Abbreviations: IQR, interquartile range; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; HAIC, hepatic arterial infusion chemotherapy; PVTT, portal vein tumor thrombosis; HVTT, hepatic vein tumor thrombus.

levels were measured at 316.0 (20.7–3621.0) ng/mL. Post-treatment, AFP levels were 81.2 (8.9–1745.0) ng/mL at 4 weeks and 32.4 (4.5–934.0) ng/mL at 8 weeks. It is important to mention that AFP assay data were missing for 8 patients within the 8 weeks.

Upon classifying patients based on early AFP response (>20% decrease in AFP within 4 weeks) and AFP response (>75% decrease in AFP within 8 weeks), we observed that patients in the early AFP response group were older [54 (49–64) years vs. 50 (43–55) years, $p = 0.026$] and exhibited lower neutrophil counts [3.09 (2.17–4.48) $*10^9$/L vs. 4.34 (3.09–7.38) $*10^9$/L, $p = 0.006$]. However, no statistical differences were observed in the baseline characteristics between the AFP-responder and non-responder groups (Table 1).

Therapeutic Response

In accordance with the RECIST v1.1 criteria, no CR was observed. Sixteen (25.4%) patients achieved PR, 39 (61.9%) patients had SD, and 8 (12.7%) patients experienced progressive disease (PD). The ORR was 25.4%, and the DCR was 87.3% (Table 2). Meanwhile, based on mRECIST criteria, the CR, PR, SD, and PD were 4 (6.3%), 32 (50.8%), 19 (30.2%), and 8 (12.7%), respectively, with an ORR and DCR of 57.1% and 87.3%, respectively (Table S1).

The median OS was not reached, and the 95% CI for OS was not available (Figure 1a). For all patients, the median PFS was 8.3 months (95% CI, 3.0–13.6 months, Figure 1b). OS was stratified according to the patient response to HAIC combined with lenvatinib and camrelizumab. Based on RECIST v1.1 criteria, patients achieving CR or PR and those with SD demonstrated significantly better OS compared to those with PD ($p < 0.001$ and $p < 0.001$, respectively, Figure 2a). However, there was no significant difference in OS between CR or PR and SD ($p = 0.301$, Figure 2a), nor between patients who achieved ORR and those who did not ($p = 0.110$, Figure 2c). Based on mRECIST criteria, OS was also better in patients who achieved CR or PR and SD compared to those with PD ($p < 0.0001$ and $p = 0.040$, respectively, Figure 2b). Additionally, the OS of patients who achieved CR or PR was significantly better than that of patients with SD ($p = 0.036$, Figure 2b), and the OS of patients who achieved ORR was significantly better than that of patients who did not ($p < 0.001$, Figure 2d).

AFP Response and Patient Outcomes

As depicted in Figure 3, we assessed the correlation between AFP response and treatment response. Our results indicated no significant difference in treatment response between the early AFP responder group and the early AFP non-responder group based on RECIST v1.1 criteria. However, using mRECIST criteria, there was a difference in the PR rate between the early AFP responder group and the early AFP non-responder group (58.7 vs. 29.4%, $p = 0.041$, Table 2). Whether RECIST v1.1 or mRECIST criteria were used, the AFP responder group showed a higher PR rate compared to the AFP non-responder group (45.5 vs. 15.2%, $p = 0.013$, and 72.7 vs. 42.4%, $p = 0.029$, respectively, Table 2). Moreover, the ORR in the AFP responder group exceeded that in the AFP non-responder group (45.5 vs. 18.2%, $p = 0.014$, and 81.8 vs. 48.5%, $p = 0.013$, respectively, Table 2).

Both early AFP response and AFP response were associated with OS and PFS. The early AFP responder group exhibited a significantly superior median OS compared to the early AFP non-responder group (not reached vs. 8.0 months, $p < 0.001$, Figure 4a). Concerning PFS, the early AFP responders group demonstrated a median PFS of 13.3 months, whereas the early AFP non-responders group had a median PFS of 3.5 months ($p = 0.018$, Figure 4b). Similarly, the AFP responders exhibited a significantly better median OS compared to the non-responders (not reached vs. 9.0 months, $p < 0.001$, Figure 4c). The median PFS was 19.3 months in the AFP responders group, whereas it was 5.1 months in the AFP non-responders group ($p = 0.002$, Figure 4d).

Factors Affecting OS and PFS

Univariate analysis revealed significant associations between OS and several factors, including Child-Pugh classification ($p = 0.053$), BCLC staging ($p = 0.012$), early AFP response ($p = 0.001$), and AFP response ($p = 0.003$, Table S2). Similarly, PFS demonstrated significant correlations with Child-Pugh classification ($p = 0.013$), BCLC staging ($p = 0.006$), early AFP response ($p = 0.022$), and AFP response ($p = 0.003$, Table S2). In separate multivariate analyses including these factors, both early AFP response and AFP response showed significant

Table 2 Therapeutic Response Stratified by AFP Response Within 4 Weeks

Evaluation (RECIST v1.1)	>20% AFP Decrease Within 4 Weeks			>75% AFP Decrease Within 8 Weeks			Evaluation (mRECIST)	>20% AFP Decrease Within 4 Weeks			>75% AFP Decrease within 8 Weeks		
	Yes (n = 46)	No (n = 17)	p-value	Yes (n = 22)	No (n = 33)	p-value		Yes (n = 46)	No (n = 17)	p-value	Yes (n = 22)	No (n = 33)	p-value
CR, n (%)	0 (0)	0 (0)	–	0 (0)	0 (0)	–	CR, n (%)	2 (4.3)	2 (11.8)	0.293	2 (9.1)	2 (6.1)	0.674
PR, n (%)	14 (30.4)	2 (11.8)	0.195	10 (45.5)	5 (15.2)	0.013	PR, n (%)	27 (58.7)	5 (29.4)	0.041	16 (72.7)	14 (42.4)	0.029
SD, n (%)	28 (60.9)	11 (64.7)	0.783	11 (50.0)	22 (66.7)	0.221	SD, n (%)	13 (28.3)	6 (35.3)	0.592	3 (13.6)	11 (33.3)	0.104
PD, n (%)	4 (8.7)	4 (23.5)	0.187	1 (4.5)	6 (18.2)	0.223	PD, n (%)	4 (8.7)	4 (23.5)	0.187	1 (4.5)	6 (18.2)	0.223
ORR, (%)	30.4	11.8	0.195	45.5	15.2	0.013	ORR, (%)	63.0	41.2	0.120	81.8	48.5	0.013
DCR, (%)	91.3	76.5	0.195	95.5	81.8	0.223	DCR, (%)	91.3	76.5	0.195	95.5	81.8	0.223

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, Objective response rate; DCR, Disease control rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors; AFP, alpha-fetoprotein.
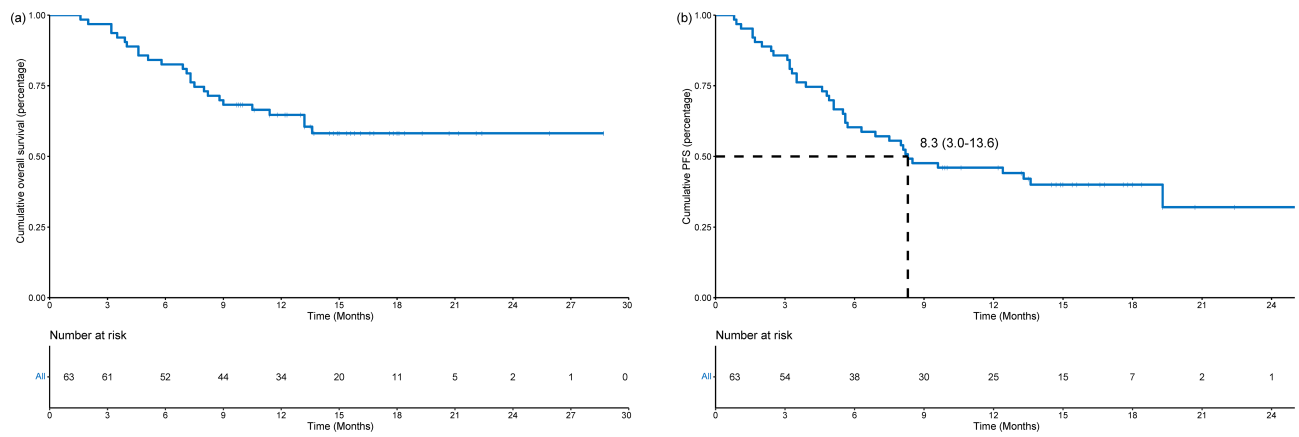
Figure 1 Kaplan–Meier curve analysis of OS (**a**) and PFS (**b**) for all patients.
Abbreviations: OS, overall survival; PFS, progression-free survival.
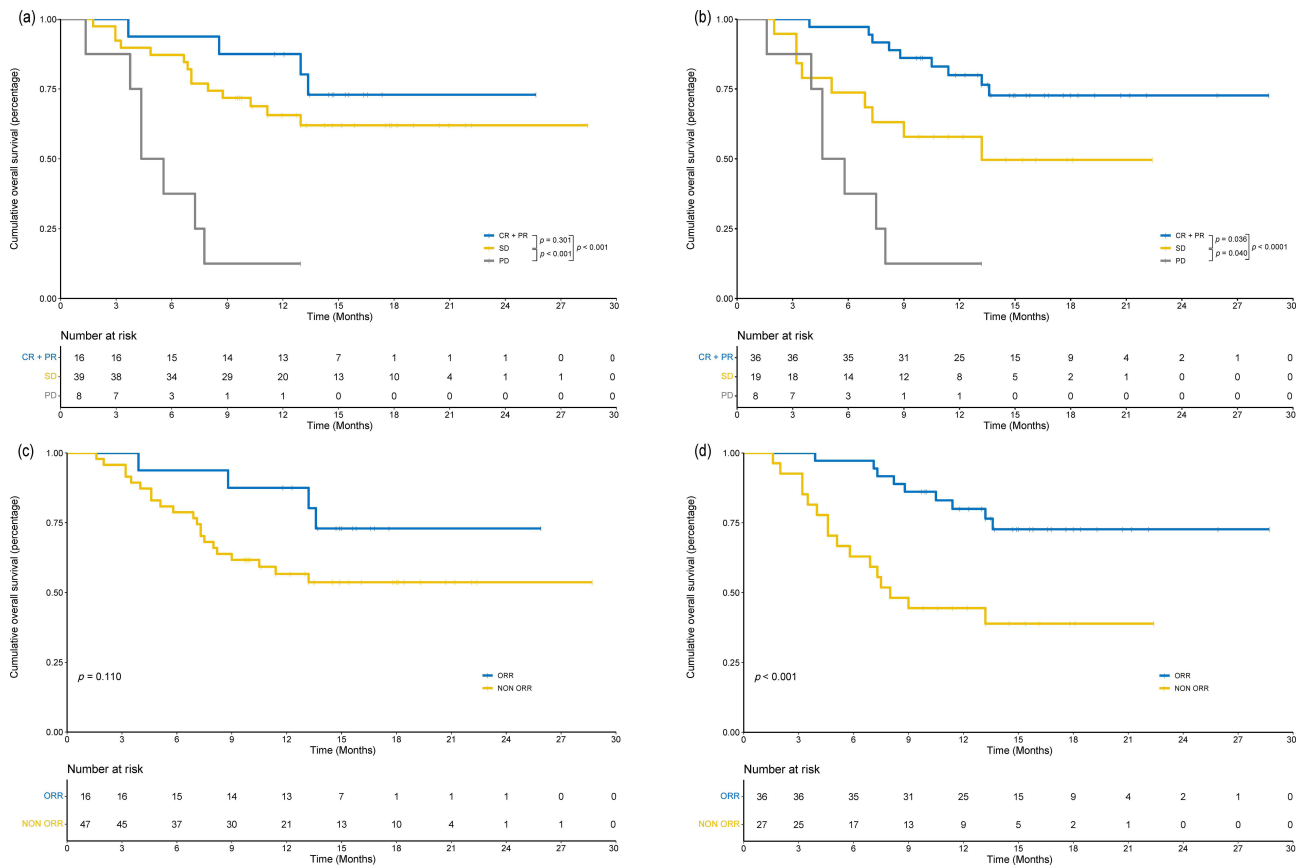

Figure 2 Kaplan–Meier curve analysis of OS among patients with CR/PR, SD, and PD according to RECIST v1.1 (**a**) and mRECIST (**b**). Kaplan–Meier curve analysis of OS among patients with ORR and non-ORR according to RECIST v1.1 (**c**) and mRECIST (**d**).
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, Objective response rate; OS, overall survival; PFS, progression-free survival.

associations with OS [hazard ratio (HR), 2.963; 95% CI, 1.333–6.585; $p = 0.008$, and HR, 6.182; 95% CI, 1.780–21.466; $p = 0.004$, Table 3]. Additionally, AFP response at 4 weeks and AFP response at 8 weeks were significantly associated with PFS (HR, 2.186; 95% CI, 1.107–4.318; $p = 0.024$, and HR, 3.078; 95% CI, 1.407–6.730; $p = 0.005$, Table 3).
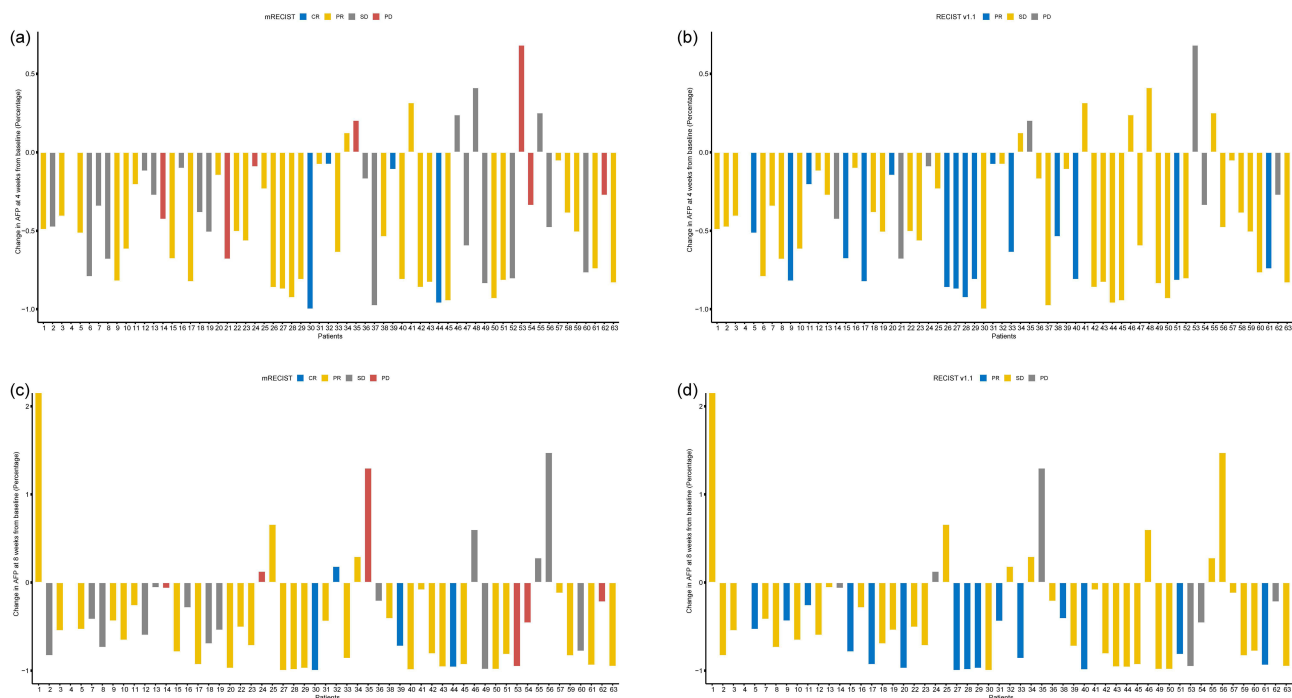
Figure 3 Waterfall plot of change in AFP at 4 weeks from baseline and best response according to mRECIST (**a**) and RECIST v1.1 (**b**), and change in AFP at 8 weeks from baseline and best response based on mRECIST (**c**) and RECIST v1.1 (**d**).
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; AFP, alpha-fetoprotein.

Subsequent Treatment After the Progression

By the end of the follow-up period, imaging progression was observed in 32 patients. Among them, 8 patients underwent vascular intervention, with 2 of them also experiencing a substitution of lenvatinib with regorafenib. Furthermore, 5 patients had lenvatinib replaced with regorafenib, 1 had lenvatinib replaced with tislelizumab, 4 underwent surgery or local ablation, and 2 underwent radiation therapy. Additionally, seven patients received only optimal supportive care due to their inability to tolerate follow-up treatment. Information on follow-up treatment was available for five other patients (Table S3).

Discussion

AFP, a member of the albumin superfamily, was expressed in 60–80% of HCC, making it a widely used diagnostic and prognostic biomarker, and persistent high AFP expression often indicates a high HCC tumor load.[17,34] We defined early AFP response as an AFP decrease of > 20% within 4 weeks, and AFP response as an AFP decrease of > 75% within 8 weeks, based on previous studies.[21,25] The results demonstrated that both early AFP response and AFP response were associated with improved OS and PFS compared to non-responders. Furthermore, multivariate analysis revealed that both early AFP response and AFP response were independent predictors of OS and PFS. Additionally, patients with better treatment response, assessed by the mRECIST criteria, experienced greater OS benefits, although no significant differences in OS were observed between the ORR and non-ORR groups according to the RECIST v1.1 criteria. While Shao et al[18] reported improved ORR and DCR in early AFP responders compared to early AFP non-responders (73% vs. 14%, $p < 0.001$, and 80% vs. 46%, $p = 0.033$), our study did not replicate these findings. However, our study demonstrated that the ORR of AFP responders was significantly superior to that of AFP non-responders, as assessed by both RECIST v1.1 and mRECIST criteria. No significant difference was observed in DCR between AFP responders and non-responders.

Although the utilization of AFP as a standalone screening tool for HCC in the general population remains controversial, AFP has consistently served as a widely utilized prognostic marker for HCC patients over several
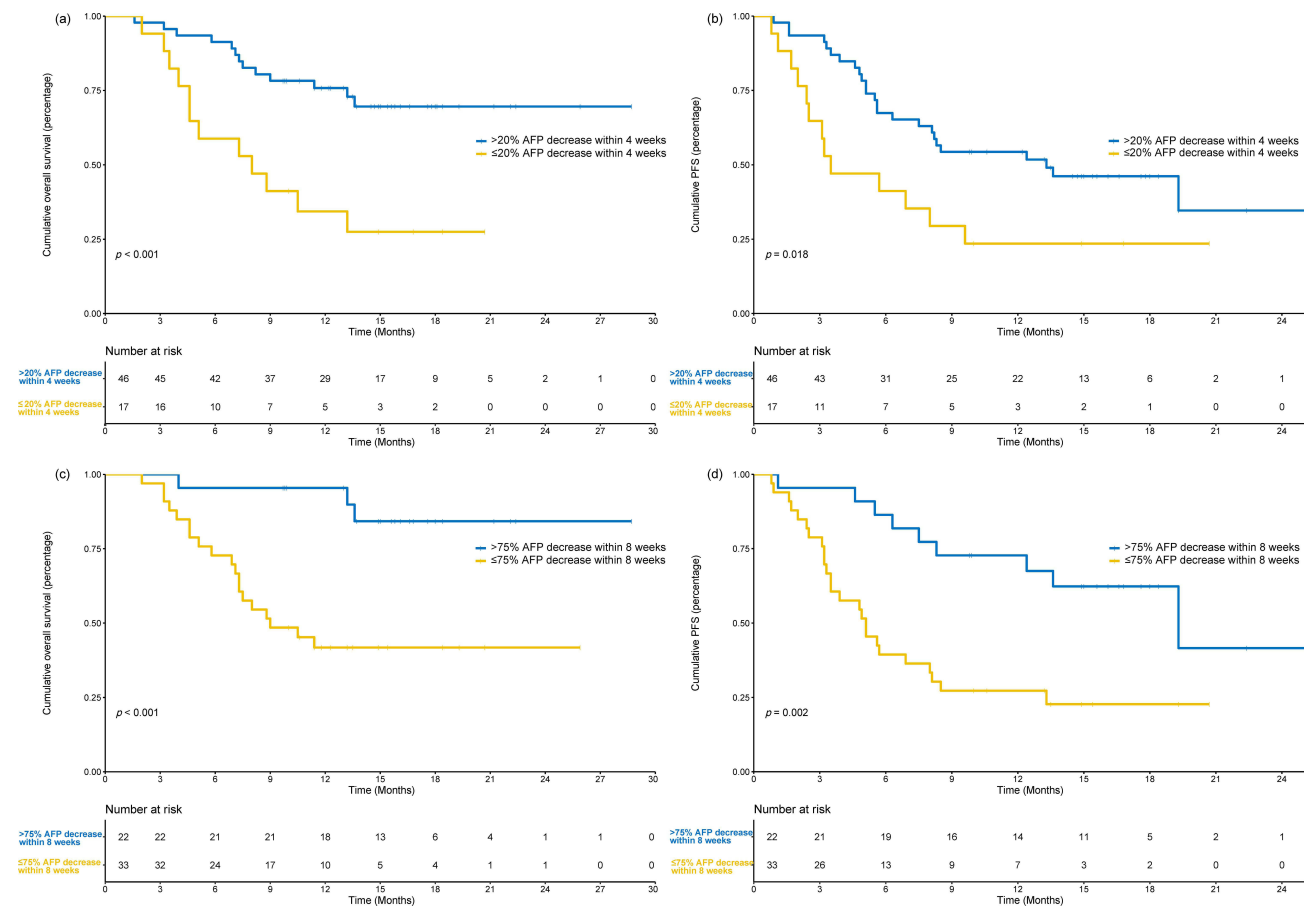
Figure 4 Kaplan–Meier curve analysis of OS (**a**) and PFS (**b**) in patients who achieved >20% decrease in AFP within 4 weeks. Kaplan–Meier curve analysis of OS (**c**) and PFS (**d**) in patients who achieved >75% decrease in AFP within 8 weeks.
Abbreviations: AFP, alpha-fetoprotein; OS, overall survival; PFS, progression-free survival.

decades.[17] Notably, AFP response during treatment has emerged as a valuable prognostic biomarker in HCC. A study conducted by Saeki et al demonstrated that patients with advanced HCC who received HAIC and achieved a ≥20% decrease in AFP levels after 2 weeks of treatment exhibited improved OS.[35] Similar findings have been validated in various studies investigating treatments such as sorafenib, ramucirumab, and atezolizumab plus bevacizumab.[21,36,37] However, it is worth noting that different cut-off values for AFP response have been employed across these studies. In addition to AFP, alterations in other commonly observed tumor markers during treatment have proven to be reliable predictive markers for the therapeutic efficacy of certain malignancies. For instance, reductions in carcinoembryonic antigen and cytokeratin fragments have been established as dependable biomarkers for assessing treatment response in patients with non-small cell lung cancer undergoing immunotherapy.[38] Therefore, it is reasonable to speculate that the reduction of AFP levels during treatment may also serve as a predictive factor for the prognosis of HCC patients receiving HAIC combined with lenvatinib and camrelizumab. Furthermore, previous studies have predominantly evaluated AFP response at a single time point or over a duration of 4 or 8 weeks. In contrast, our study conducted a consecutive assessment of AFP response within 4 and 8 weeks, thereby providing a more comprehensive evaluation of its prognostic significance within the context of this treatment combination for u-HCC.

Despite several preclinical investigations into the genetic regulation of AFP, the underlying mechanism responsible for its overexpression in HCC remains elusive. HCC was a malignancy highly dependent on vascularization, with vascular endothelial growth factor (VEGF) playing a crucial role. Numerous studies have indicated that aberrant AFP expression interacts with angiogenesis processes in HCC. Moreover, in vitro assays have demonstrated that silencing AFP leads to the inhibition of VEGF production in HCC cells.[17] Furthermore, AFP has the capacity to modulate the

Table 3 Multivariate Analysis of Factors That Influenced OS and PFS

Characteristics	Overall Survival			Progression-Free Survival			Overall Survival			Progression-Free Survival		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Child-Pugh classification (A/B)	3.065	1.098–8.550	0.032	4.053	1.667–9.855	0.002	2.957	0.958–9.126	0.059	2.871	1.068–7.720	0.037
BCLC (A+B/C)	3.849	1.286–11.519	0.016	2.895	1.328–6.312	0.008	6.583	1.514–28.625	0.012	3.416	1.385–8.427	0.008
AFP response within 4 weeks (Yes/no)	2.963	1.333–6.585	0.008	2.186	1.107–4.318	0.024	-	–	–	–	–	–
AFP response within 8 weeks (Yes/no)	–	–	–	–	–	–	6.182	1.780–21.466	0.004	3.078	1.407–6.730	0.005

Abbreviations: HR, hazard ratio; CI, confidence interval; BCLC Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; OS, overall survival; PFS, progression-free survival.

immune microenvironment of HCC through various mechanisms. It enables malignant cells to evade immune surveillance by impeding dendritic cell maturation and inducing apoptosis. Additionally, AFP exacerbates the immunosuppressive state of HCC by influencing the balance of T cell subsets (CD4$^+$ and CD8$^+$) and inducing lymphocyte death.[39] Thus, elevated AFP levels often indicate a higher tumor burden, more severe vascular abnormalities, and increased immunosuppression in HCC patients. Chemotherapeutic agents administered during HAIC can effectively eliminate tumor cells, thereby reducing the overall tumor load.[40] Lenvatinib, functioning as a molecularly targeted drug, exerts its anti-VEGF effect, impeding the formation of aberrant blood vessels in HCC.[4,41] Simultaneously, camrelizumab, acting as an immune checkpoint inhibitor, contributes to ameliorating the state of immunosuppression in HCC.[4,41] This immune modulation enhances immune surveillance, resulting in a further reduction of the tumor load. Additionally, the direct cytotoxic effects of chemotherapeutic agents during HAIC expose tumor cell antigens, synergistically augmenting the antitumor efficacy of camrelizumab.[42] The anti-VEGF impact of lenvatinib induces dendritic maturation, modifies the ratio of M1 to M2 macrophage subtypes, diminishes Treg cell accumulation, elevates the abundance of cytotoxic T cells, and reduces immune suppression.[42] This cascade of events culminates in tumor cell death, necrosis, increased release of tumor antigens, and heightened tumor immunogenicity. The synergistic interaction among HAIC, lenvatinib, and camrelizumab leads to tumor cell necrosis, vascular normalization, and restoration of normal immune surveillance. This combined therapeutic approach effectively reduces tumor-derived AFP levels and thus regulates the abnormal state of HCC.

In this study, we observed that Child-Pugh class B was an independent risk factor for both OS and PFS in HCC patients. The severity of cirrhosis directly correlates with poorer liver function, which is associated with a worse prognosis.[43] Furthermore, we found that early AFP responders exhibited lower neutrophil counts compared to early non-responders. Neutrophils have been implicated in inhibiting the proliferation and cytotoxicity of T-lymphocytes, promoting the infiltration of immunosuppressive cells, and inducing stemness in cancer cells.[44] Consequently, malignant cells can evade immune surveillance. Therefore, the lower neutrophil count observed in early AFP responders may contribute to their better prognosis.

The present study has several limitations that should be acknowledged. Firstly, it is important to note that this study is a single-center retrospective study, which inherently carries limitations in terms of generalizability and potential bias. The sample size was relatively small, and there were missing AFP data in some patients, which could affect the accuracy and representativeness of the findings. Secondly, the majority of patients included in this study were hepatitis B-related HCC patients, and it remains uncertain whether the results can be extrapolated to other etiologies such as hepatitis C or steatohepatitis-related HCC. Therefore, caution should be exercised when applying the findings to these populations. Furthermore, although we collected data on second-line treatments after progression, we were unable to assess OS among different second-line treatment regimens due to the large number of regimens and missing information in some cases. Finally, although we evaluated different AFP cut-off values at different time points, the applicability of these findings to other treatment regimens requires further confirmation through well-designed multicenter and prospective randomized studies.

Conclusion

In conclusion, this study demonstrated that patients with u-HCC who received combination therapy with HAIC, lenvatinib, and camrelizumab experienced improved OS and PFS when achieving a decrease in AFP levels of more than 20% within 4 weeks and more than 75% within 8 weeks of treatment initiation. These findings suggest the efficacy of the HAIC, lenvatinib, and camrelizumab combination therapy in the treatment of u-HCC.

Abbreviations

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; DCR, disease control rate; HAIC, hepatic arterial infusion chemotherapy; HCC, Hepatocellular carcinoma; HR, hazard ratio; HVTT, hepatic vein tumor thrombus; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PVTT, portal vein tumor thrombosis; SD, stable disease; u-HCC, unresectable hepatocellular carcinoma; VEGF, vascular endothelial growth factor.

Data Sharing Statement

The data that support the results of this study are obtainable upon request from the corresponding author.

Ethics Statement

The Ethics Committee of the First Affiliated Hospital, Jiangxi Medical College, Nanchang University reviewed and granted approval for this study (Approval No. (2022) CDYFYYLK (06-009)).

Patient Consent for Publication

Informed consent was exempted due to the retrospective nature of the study, and the absence of patient-identifiable information.

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Disclosure

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