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ORIGINAL RESEARCH

Efficacy of Locoregional HAIC and Systemic Treatment for Treatment- Naive Unresectable Hepatocellulcar Carcinoma

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Background and Aim: Unresectable hepatocellular carcinoma (u-HCC) is highly heterogeneous, with limited survival expectancy. The aim of this study was to reappraise the efficacy and safety of locoregional hepatic arterial infusion chemotherapy (HAIC) combined with systemic treatment in initially diagnosed u-HCC.

Methods: A total of 302 treatment-naive patients with u-HCC who received HAIC and systemic treatment therapy between December 2018 and November 2023 were enrolled. The cumulative progression-free survival (PFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method. Factors affecting survival were analyzed via Cox regression analysis.

Results: The median PFS and OS were 11.5 (95% CI: 8.7–14.3) months and 30.0 (95% CI: 20.7–39.2) months, respectively. The estimated PFS rates were 66.2%, 47.9% and 35.2% at 0.5, 1 and 2 years, respectively, and the estimated OS rates were 68.0%, 52.5% and 41.7% at 1, 2, and 3 years, respectively. Aspartate aminotransferase (AST), alkaline phosphatase (ALP), neutrophil to lymphocyte ratio (NLR), extrahepatic metastasis (EHM), metabolic comorbidity and treatment allocation were identified as factors associated with patient survival. The treatment regimen was well tolerated.

Conclusion: Locoregional HAIC combined with systemic immune checkpoint inhibitors (ICIs) and targeted therapy represents an effective and safe treatment modality for initially diagnosed u-HCC. Favorable survival outcomes were associated with AST ≤ 56.5 U/L, ALP ≤ 174.5 U/L, NLR ≤ 1.77, absence of extrahepatic metastasis, presence of metabolic comorbidity, and HAIC combined with ICI plus targeted/anti-VEGF therapy. These findings require further validation in external and prospective cohorts.

Keywords: unresectable hepatocellular carcinoma, systemic therapy, hepatic arterial infusion chemotherapy

Introduction

Hepatocellular carcinoma (HCC) constitutes a major cancer burden worldwide.[1] Due to its insidious development nature, a large number of patients are diagnosed at an advanced stage which is unsuitable for radical treatments such as surgery and ablation. Additionally, some patients with infiltrative large tumors, obvious hepatic arterial-portal or hepatic vein shunt, or major portal vein tumor thrombosis (PVTT) are ineligible for transcatheter arterial chemoembolization (TACE).[2]

Tyrosine kinase inhibitor (TKI) sorafenib was approved in 2008 for the treatment of advanced HCC, followed a decade later by lenvatinib.[3,4] However, in patients with major PVTT, the median overall survival (OS) after TKI treatment is approximately 6.0 months.[5] With the advent of immunotherapy, systemic regimens such as atezolizumab plus bevacizumab, tremelimumab plus durvalumab, and sintilimab plus a bevacizumab biosimilar have been approved as preferred first-line options for advanced HCC.[6–8] Due to the increased risk of variceal bleeding related to major PVTT,

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most clinical trials excluded such patients. Given that the median OS of patients with major PVTT in the IMbrave150 trial was only 7.6 months, more effective approaches are warranted.[6]

Hepatic arterial infusion chemotherapy (HAIC) directly delivers chemotherapeutic agents into the tumor-feeding artery, achieving tumor shrinkage with lower systemic toxicity by taking advantage of the "first pass effect" of the liver.[9,10] In scenarios where TACE is unsuitable, such as infiltrative large tumors, obvious hepatic arterial-portal or hepatic vein shunt, or major PVTT, HAIC has been proven safe and effective, either as monotherapy or in combination with sorafenib.[11–14] However, no Phase III randomized trials have yet provided evidence of the benefits of HAIC combined with immune checkpoint inhibitors (ICIs) and targeted therapy in unresectable HCC (u-HCC), indicating a need for further studies.

In this study, we aimed to evaluate the efficacy and safety of locoregional HAIC combined with ICIs and targeted therapy in treatment-naive u-HCC, and to identify factors contributing to improved patient survival.

Patients and Methods

Patients

In this retrospective study, we enrolled treatment-naive u-HCC patients who received HAIC combined with ICIs targeting programmed cell death-1 (PD-1) or its ligand (PD-L1), as well as targeted therapy with TKIs or an anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, between December 2018 and November 2023 at our department. The end date of follow-up was on December 31, 2024. The study flow chart is summarized in Figure 1.

The inclusion criteria were as follows: (1) aged ≥18 years; (2) pathologically or radiologically diagnosed HCC according to the American Association for the Study of Liver Diseases (AASLD) practice guideline, characterized with infiltrative large tumors, bi-lobar multifocal HCC, obvious hepatic arterial-portal or hepatic vein shunt, or major PVTT; (3) patients who received HAIC and systemic ICIs or targeted therapy (TKIs or anti-VEGF antibody); (4) no prior treatment for HCC; (5) Child-Pugh A or B, and Eastern Cooperative Oncology Group Performance Status (ECOG PS)

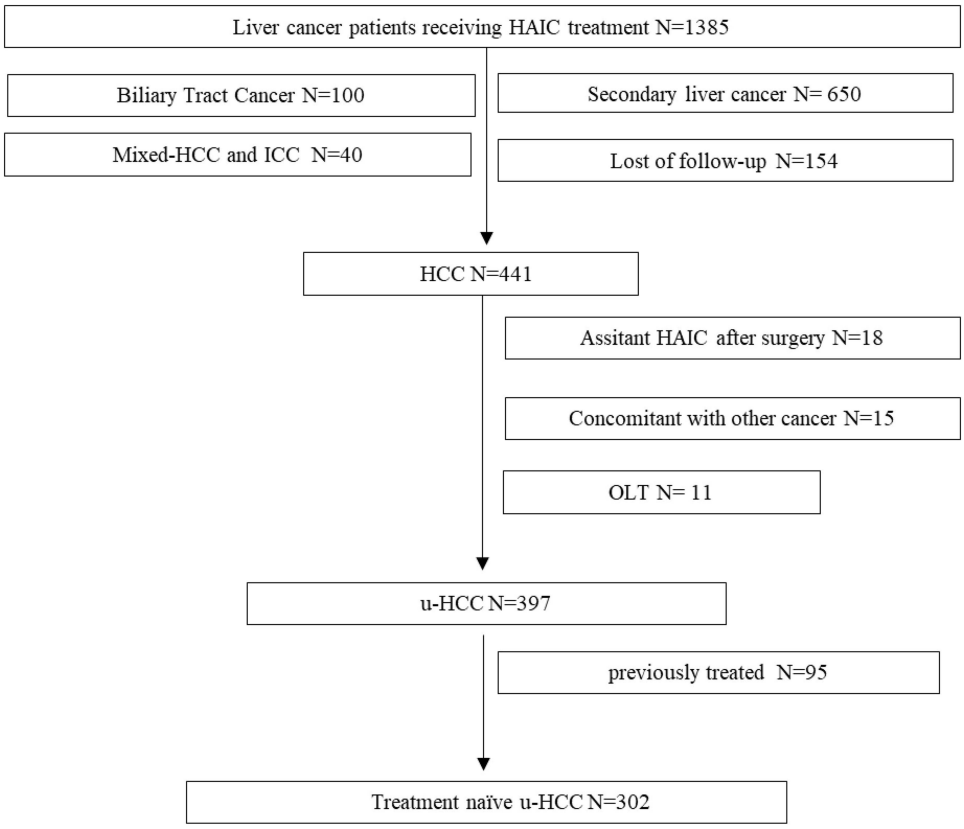

Figure 1 Flow chart of enrolled treatment-naive patients with unresectable HCC. OLT: orthotopic liver transplantation.

score of 0–1; (6) no other malignancies within five years; (7) patients who received at least two cycles of HAIC; (8) availability of complete medical records and follow-up data.

The main exclusion criteria were as follows: (1) pathologically diagnosed as fibrolamellar HCC, sarcomatous HCC, or combined hepatocellular cholangiocarcinoma; (2) active upper gastrointestinal bleeding or coagulation dysfunction; (3) impaired function of major organs; (4) lack of laboratory tests and imaging evaluations (CT or MRI) obtained within a month before the initial treatment. Written informed consent for the treatments was obtained from each patient. Electronic medical records were used to collect clinical information, imaging data and laboratory results for all patients. only patients with complete data for the variables of interest were included in the primary analysis.

Treatment Procedures

HAIC was performed as previously reported.[15] The selection of HAIC was based on the tumor characteristics, including infiltrative large or bi-lobar multifocal HCC, presence of major PVTT at contrast-enhanced MRI or CT imaging, or evidence of obvious hepatic arterioportal or hepatic vein shunt on hepatic arterial digital subtraction angiography. The FOLFOX-HAIC regimen was administrated as follows: Oxaliplatin 85 mg/m^2 infused for 2 hours, leucovorin 400 mg/m^2 for 2 hours, 5-fluorouracil 1,200 mg/m^2 over 23 hours or 2400 mg/m^2 for 46 hours via a pump, depending on patient's general status, liver function, and platelet count. Repeated HAIC cycles were scheduled at intervals of 3–4 weeks based on the physician's evaluation and treatment response.

Systemic treatment was initiated on the second day after HAIC if the patients tolerated HAIC well. The choice of ICIs and targeted therapy was made through joint discussion among attending physicians, taking into consideration tumor characteristics, the patient's general conditions, standard cares recommended by national guidelines, and the patient's preferences in real-world practice. The prescribed systemic medications include atezolizumab and bevacizumab, sintilimab plus a bevacizumab biosimilar, camrelizumab plus rivoceranib, orally administered TKIs such as lenvatinib and sorafenib, and ICIs such as sintilimab, tislelizumab or pembrolizumab. If the patient was intolerant to HAIC-related toxicities, systemic treatment was postponed until symptoms resolved.

Adverse events (AEs) of grade 1 or 2 were managed without treatment modification. For grade ≥ 3 AEs, the regimen was discontinued until the AEs resolved or improved.

Treatment Response Assessment and Survival Outcomes

Contrast-enhanced CT or MRI was performed every two HAIC cycles. The best tumor response was evaluated by two investigators according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and the modified RECIST (mRECIST) criteria. Discrepancies between the two criteria were resolved by consensus review through at least two independent radiologists who were blinded to patient's clinical information. For discrepant cases, a joint re-evaluation was conducted, and a final unified response classification was determined through discussion and mutual agreement based on the overall imaging features and lesion characteristics. If consensus could not be reached immediately, a third senior radiologist was consulted to make the final decision. The unified response outcome was then used as the final response classification in subsequent analyses.

OS was defined as the interval from the start of treatment to the day of death from any cause or the last follow-up. Progression-free survival (PFS) was defined as the time from the treatment initiation to the first occurrence of tumor progression or death from any cause, whichever came first. AEs during treatment were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range, IQR). Categorical variables were presented as counts and percentages. The Kaplan–Meier method was used for analyzing the time-to-event variables (OS and PFS), and differences between groups were compared using the Log rank test. Univariable and multivariable Cox regression analyses were performed to identify factors associated with survival outcomes. Variables with a P value < 0.05 in the univariable analysis were entered into the multivariable analysis. A two-sided $P < 0.05$ was considered as statistically significant.

Results

Patient Characteristics

A total of 302 patients were included in the final analysis. Baseline patient characteristics are summarized in Table 1. There were 274 males (90.7%) and 28 females (9.3%), with a mean age of 56.9 years (range, 26–88). Hepatitis B virus

Table 1 The Baseline Characteristics and Treatment Allocation of Initially Diagnosed u-HCC Patients

Variable	NO. (%)
Gender	
Male	274(90.7%)
Female	28(9.3%)
Age (years)	56.9±11.1
Etiology	
HBV	284(94.0%)
HCV	9(3.0%)
Alcohol	3(1.0%)
Others	6(2.0%)
TB (μM)	16.3±8.4
ALT (U/L)	51.9±31.3
AST (U/L)	82.1±60.0
ALP (U/L)	192.6±124.7
GGT (U/L)	236.3±174.5
PLT (x 10^9/L)	179.2±92.0
PT (second)	13.2±1.1
AFP (ng/mL)	14883.4±23,430.5
PIVKA-II (mAU/mL)	29218.3±32,359.6
CRP (mg/L)	25.5±31.1
NLR	3.45±1.90
Child-Pugh stage	
A	251(83.1%)
B	51(16.9%)
Tumor size (mm)	109.1±41.2
Tumor stage (CNLC)	
IIA	6(2.0%)
IIB	7(2.3%)
IIIA	194(64.2%)
IIIB	95(31.5%)
Arterio-portal/venous shunt	
Without	204(67.5%)
With	98(32.5%)
Metabolic comorbidity	
Without	172(57.0%)
With	130(43.0%)
Treatment	
HAIC + TKIs or ICIs	49(16.2%)
HAIC + ICIs + TKIs/anti-VEGF antibody	253(83.8%)

Abbreviations: u-HCC, unresectable hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; PLT, platelet; PT, prothrombin time; CRP, c-reactive protein; NLR, neutrophil to lymphocyte ratio; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CNLC, China Liver Cancer Staging; TKI, tyrosine kinase inhibitor; ICIs, immune checkpoint inhibitors; HAIC, hepatic arterial infusion chemotherapy.

(HBV) infection was predominant (284/302, 94.0%), and 251 (83.1%) of the patients were Child-Pugh class A. According to the China Liver Cancer (CNLC) staging system, 13 patients (4.3%) were classified as CNLC IIA/B and 289 (95.7%) as CNLC IIIA/B; 95 patients (31.5%) had extrahepatic metastasis (EHM). In addition, 130 patients (43.0%) had one or more metabolic comorbidities, such as hypertension, type 2 diabetes, or cardiovascular diseases. Among the systemic regimens, 36 patients (11.9%) received only TKIs as initial systemic medication, 13 (4.3%) received monotherapy with an ICI, 158 (52.3%) received TKIs in combination with an ICI, and 95 (31.5%) received atezolizumab and bevacizumab or sintilimab plus a bevacizumab biosimilar.

Treatment Response Assessment

Treatment response was evaluated according to the RECIST 1.1 and mRECIST criteria. In accordance with the RECIST 1.1 criteria, 6 patients (2.0%) achieved complete response (CR), 189 (62.6%) had partial response (PR), 57 (18.9%) had stable disease (SD), and 50 (16.6%) had progressive disease (PD) as the best treatment response. The objective response rate (ORR) per RECIST 1.1 was 64.6%, and the disease control rate (DCR) was 83.4%. According to the mRECIST criteria, 30 patients (9.9%) achieved CR, 175 (57.9%) had PR, and 50 (16.6%) had SD, and 47 (15.6%) had PD. The ORR per mRECIST was 67.9% and DCR was 84.4% (Table 2).

For patients who experienced disease progression, the second-line systemic regimens varied: 24 patients received monotherapy with a targeted agent or an ICI, 105 patients received an ICI combined with targeted therapy, and 75 patients received best supportive care due to worsened performance status or Child-Pugh score.

Survival Outcomes

As of December 31, 2024, the median follow-up time was 19.5 months (IQR, 18.7–20.3). The median PFS was 11.5 months (95% CI,8.7–14.3). The estimated PFS rates at 6, 12, and 24 months were 66.2%, 47.9%, and 35.2%, respectively. (Figure 2). During the follow-up period, 131 patients died. The median OS was 30.0 months (95% CI, 20.7–39.2). The estimated OS rates at 1, 2, and 3 years were 68.0%, 52.5%, and 41.7%, respectively (Figure 2).

Factors Associated with PFS and OS

In univariable analysis, variables associated with tumor progression included etiology ($P = 0.049$), total bilirubin (TB) ($P = 0.030$), aspartate aminotransferase (AST) ($P < 0.001$), alkaline phosphatase (ALP) ($P < 0.001$), γ-glutamyl transferase (GGT) ($P = 0.001$), CRP ($P = 0.001$), neutrophil to lymphocyte ratio (NLR) ($P = 0.010$), Child-Pugh grade ($P < 0.001$), arterioportal or venous shunt ($P = 0.048$), EHM ($P = 0.004$), metabolic comorbidity ($P = 0.001$) and systemic treatment modality ($P = 0.014$) (Table 3). Multivariable analysis showed that AST ($P = 0.014$), ALP ($P = 0.002$), NLR ($P = 0.007$), Child-Pugh grade ($P = 0.031$), EHM ($P < 0.001$), metabolic comorbidity ($P = 0.006$) and combined systemic treatment modality ($P = 0.046$) were statistically significant for PFS (Table 3 and Figure 3).

Table 2 Tumor Response According to RECIST 1.1 and mRECIST Criteria

Tumor response	RECIST 1.1	mRECIST
CR	6(2.0%)	30(9.9%)
PR	189(62.6%)	175(57.9%)
SD	57(18.9%)	50(16.6%)
PD	50(16.6%)	47(15.6%)
ORR	195(64.6%)	205(67.9%)
DCR	252(83.4%)	255(84.4%)

Abbreviations: RECIST, response evaluation criteria in solid tumor; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

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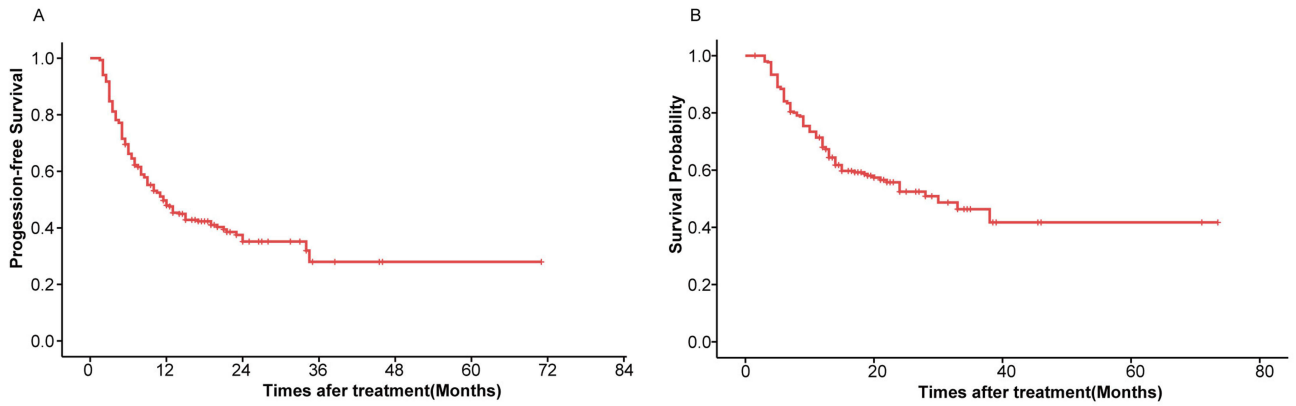

Figure 2 Kaplan-Meier curves of progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) for treatment-naive unresectable HCC patients who underwent locoregional HAIC and systemic ICIs and targeted therapy. The median OS and PFS were 30.0 months and 11.5 months, respectively.

In univariable analysis, variables associated with OS in univariable analysis included TB ($P = 0.005$), AST ($P = 0.001$), ALP ($P < 0.001$), GGT ($P = 0.001$), prothrombin time (PT) ($P = 0.006$), CRP ($P < 0.001$), NLR ($P = 0.007$), Child-Pugh grade ($P < 0.001$), arterioportal or venous shunt ($P = 0.049$), EHM ($P = 0.040$), metabolic comorbidity ($P = 0.001$), and combined systemic treatment modality ($P = 0.003$) (Table 4). Multivariable analysis showed that total bilirubin ($P = 0.047$),

Table 3 Univariate and Multivariate Analysis of Factors Associated with Progression-Free Survival

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Gender (Female vs. Male)	0.979	0.602–1.595	0.933			
Etiology (Viral vs. Non-viral)	4.051	1.004–16.335	0.049			
Age (≤ 58 vs.>58 years)	1.081	0.789–1.482	0.627			
TB (≤ 14.5 vs.>14.5μmol/L)	1.473	1.039–2.087	0.030			
Albumin (≤ 40 vs.>40 g/L)	1.294	0.703–2.384	0.407			
ALT (≤ 42 vs.>42 U/L)	1.481	0.970–2.260	0.069			
AST (≤ 56.5 vs.>56.5 U/L)	1.804	1.322–2.461	<0.001	1.514	1.087–2.109	0.014
ALP (≤ 174.5 vs.>174.5 U/L)	1.828	1.362–2.453	<0.001	1.609	1.183–2.189	0.002
GGT (≤ 188.5 vs.>188.5 U/L)	0.587	0.434–0.795	0.001			
PT (≤ 13.1 vs.>13.1 second)	1.301	0.969–1.747	0.080			
AFP (≤ 48 vs.>48 ng/mL)	1.228	0.861–1.752	0.256			
PIVKA-II (≤ 46 vs.>46 mAU/mL)	1.909	0.608–5.989	0.268			
CRP (≤ 16.5 vs.>16.5 mg/L)	1.771	1.321–2.374	0.001			
NLR (≤ 1.77 vs.>1.77)	1.965	1.175–3.285	0.010	2.051	1.218–3.454	0.007
Child-Pugh score (A vs. B)	0.007	1.490–3.004	<0.001	1.506	1.038–2.185	0.031
Tumor diameter (≤ 110 vs.>110 mm)	1.325	0.988–1.776	0.060			
Tumor stage (CNLC IIA/IIB vs. IIIA/IIIB)	2.363	0.877–6.371	0.089			
Arterio-portal/venous shunt (Without vs. With)	1.358	1.002–1.839	0.048			
EHM (Without vs. With)	1.570	1.159–2.218	0.004	1.805	1.320–2.470	<0.001
Metabolic comorbidity (Without vs. With)	0.582	0.428–0.790	0.001	0.645	0.472–0.880	0.006
Treatment mode (HAIC + TKIs or ICIs vs. HAIC + ICIs + TKIs/anti-VEGF antibody)	0.615	0.417–0.908	0.014	0.667	0.447–0.993	0.046

Abbreviations: TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; PT, prothrombin time; NLR, neutrophil to lymphocyte ratio; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CNLC, China Liver Cancer; EHM, extrahepatic metastasis.

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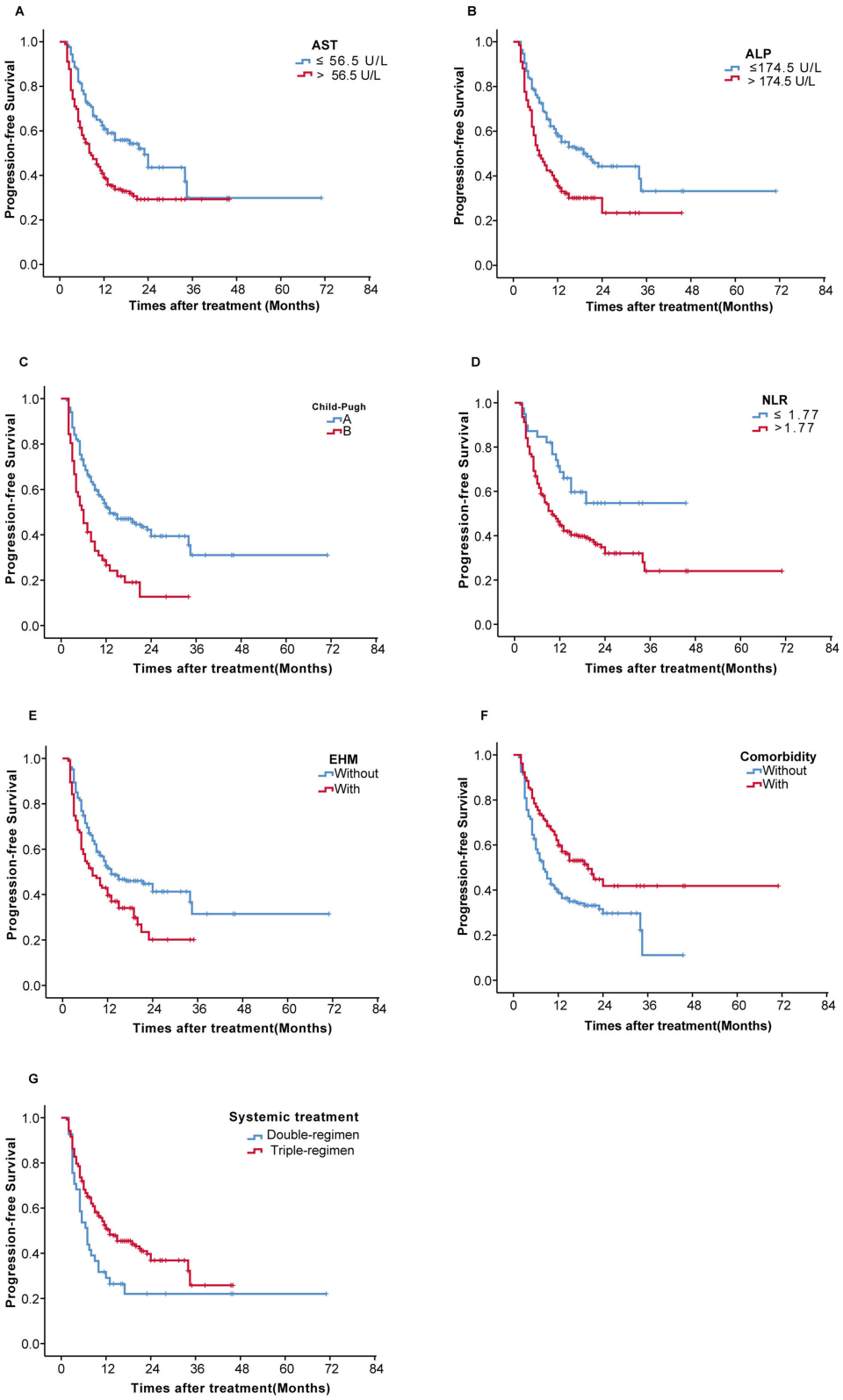

Figure 3 Kaplan-Meier curves of progression-free survival (PFS) in u-HCC patients stratified by various risk factors in univariable Cox regression analysis. (**A**) PFS according to aspartate aminotransferase (AST). AST was significantly associated with PFS ($P < 0.001$). (**B**) PFS according to alkaline phosphatase (ALP). ALP was significantly associated with PFS ($P < 0.001$). (**C**) PFS according to Child-Pugh grade. Child-Pugh grade was significantly associated with PFS ($P < 0.001$). (**D**) PFS according to neutrophil ratio-to-lymphocyte (NLR). NLR was significantly associated with PFS ($P = 0.010$). (**E**) PFS according to extrahepatic metastasis (EHM). EHM was significantly associated with PFS ($P = 0.004$). (**F**) PFS according to metabolic comorbidity. Metabolic comorbidity was significantly associated with PFS ($P = 0.001$). (**G**) PFS according to systemic treatment modality. Systemic treatment modality was significantly associated with PFS ($P = 0.014$).

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Table 4 Univariate and Multivariate Analysis of Factors Associated with Overall Survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Gender (Female vs. Male)	1.232	0.664–2.287	0.508			
Etiology (Viral vs. Non-viral)	0.193	0.027–1.378	0.101			
Age (≤ 58 vs. >58 years)	1.223	0.850–1.760	0.227			
TB (≤ 14.5 vs.>14.5 μmol/L)	1.867	1.207–2.888	0.005	1.571	1.006–2.452	0.047
Albumin (≤ 40 vs.> 40 g/L)	2.162	0.799–5.854	0.129			
ALT (≤ 42 vs. > 42 U/L)	0.462	0.171–1.252	0.151			
AST (≤ 56.5 vs.> 56.5U/L)	2.062	1.413–3.009	0.001	1.621	1.093–2.404	0.016
ALP (≤174.5 vs.>174.5 U/L)	2.380	1.677–3.376	<0.001	2.013	1.396–2.902	0.001
GGT (≤ 188.5 vs. > 188.5 U/L)	1.812	1.261–2.604	0.001			
PT (≤ 13.1 vs. >13.1 second)	1.618	1.147–2.282	0.006			
AFP (≤ 48 vs. > 48 ng/mL)	1.324	0.867–2.023	0.194			
PIVKA-II (≤ 46 vs. > 46 mAU/mL)	1.397	0.444–4.393	0.568			
CRP (≤ 16.5 vs. > 16.5 mg/L)	2.123	1.502–3.002	<0.001	1.489	1.036–2.140	0.032
NLR (≤ 1.77 vs. > 1.77)	2.529	1.284–4.982	0.007	2.324	1.160–4.657	0.017
Child-Pugh score (A vs. B)	2.350	1.580–3.494	<0.001			
Tumor diameter (≤ 110 mm vs. >110 mm)	1.306	0.926–1.841	0.128			
Tumor stage (CNLC IIA/IIB vs. IIIA/IIIB)	1.842	0.586–5.789	0.296			
Arterio-portal/venous shunt (Without vs. With)	1.426	1.002–2.030	0.049			
EHM (Without vs. With)	1.452	1.018–2.071	0.040	1.551	1.073–2.240	0.019
Metabolic comorbidity (Without vs. With)	0.545	0.378–0.786	0.001	0.622	0.428–0.904	0.013
Treatment mode (HAIC + TKIs or ICIs vs. HAIC + ICIs + TKIs/anti-VEGF antibody)	0.523	0.340–0.804	0.003	0.523	0.338–0.811	0.004

Abbreviations: TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; PT, prothrombin time; NLR, neutrophil to lymphocyte ratio; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CNLC, China Liver Cancer; EHM, extrahepatic metastasis.

AST ($P = 0.016$), ALP ($P = 0.001$), CRP ($P = 0.032$), NLR ($P = 0.017$), EHM ($P = 0.019$), metabolic comorbidity ($P = 0.013$), and combined systemic treatment modality ($P = 0.004$) were statistically significant for OS (Table 4 and Figure 4).

Prognostic Value of Objective Response

ORR has been documented to be of prognostic value in cancer survival.[16] In our cohort, ORR was significantly associated with improved PFS and OS. Patients who achieved objective response had an extended survival benefit with a median PFS of 34.0 months and median OS not reached, whereas those without an objective response had a median PFS of 4.0 months and a median OS 8.0 months, respectively (both $P < 0.001$) (Figure 5).

Safety

As listed in Table 5, the most common AEs were thrombocytopenia (25.2%), ascites (17.5%), fever (16.9%), elevated aminotransferase (14.2%), neutropenia (13.9%), hypoalbuminemia (13.2%), and elevated TB (12.9%). The most common grade 3/4 AEs were upper gastrointestinal bleeding (7.3%), elevated transaminase (7.3%), thrombocytopenia (6.3%) and elevated TB (6.3%). No treatment-related deaths occurred.

Discussion

The survival expectancy of patients with u-HCC is poor, as they typically present with infiltrative large tumors, bi-lobar multifocal nodules, major PVTT or even EHM.[4,17–19] In this study, we demonstrate that locoregional HAIC combined with systemic treatment is an effective and safe modality for treatment-naive u-HCC.

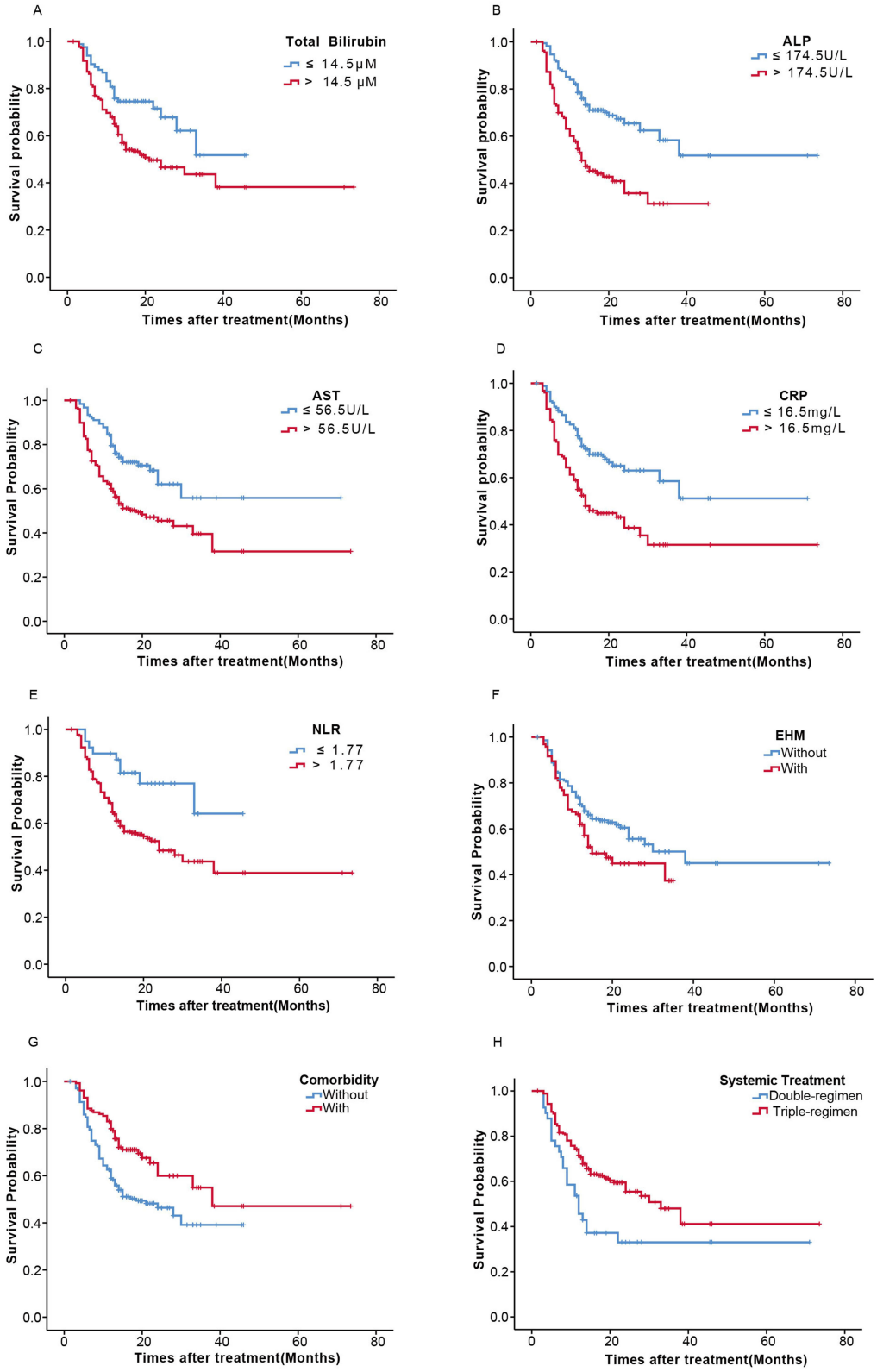

Figure 4 Kaplan-Meier curves of overall survival (OS) in u-HCC patients stratified by various risk factors in univariable Cox regression analysis. (**A**) OS according to total bilirubin (TB). TB was significantly associated with OS ($P = 0.005$). (**B**) OS according to alkaline phosphatase (ALP). ALP was significantly associated with OS ($P < 0.001$). (**C**) OS according to aspartate aminotransferase (AST). AST was significantly associated with OS ($P = 0.001$). (**D**) OS according to CRP. CRP was significantly associated with OS ($P < 0.001$). (**E**) OS according to neutrophil-to-lymphocyte ratio (NLR). NLR was significantly associated with OS ($P = 0.007$). (**F**) OS according to extrahepatic metastasis (EHM). EHM was significantly associated with OS ($P = 0.040$). (**G**) OS according to metabolic comorbidity. Metabolic comorbidity was significantly associated with OS ($P = 0.001$). (**H**) OS according to systemic treatment modality. Systemic treatment modality was significantly associated with OS ($P = 0.003$).

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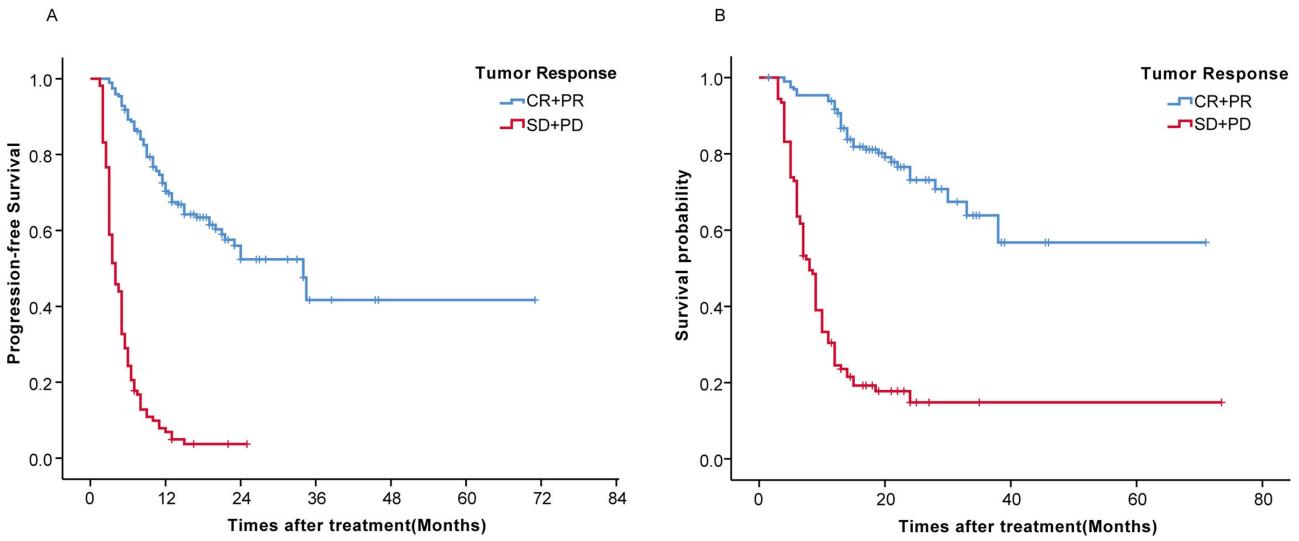

Figure 5 Kaplan-Meier curves of survival according to tumor treatment response in univariable Cox regression analysis. (**A**) Objective response (CR + PR) was significantly associated with PFS ($P < 0.001$). (**B**) Objective response (CR + PR) was statistically associated with OS ($P < 0.001$).

Guidelines for u-HCC vary worldwide. In Western countries, systemic treatments such as atezolizumab and bevacizumab, tremelimumab plus durvalumab are recommended as first-line of options, whereas in the Pacific-Asian region, locoregional treatments combined with systemic treatment have been shown to provide better survival benefit.[20–22]

Table 5 Adverse Events Graded According to CTCAE 5.0

Adverse event	Any Grade n (%)	Grades 1–2 n (%)	Grades 3–4 n (%)
Neutropenia	42(13.9)	39(12.9)	3(1.0)
Thrombocytopenia	76(25.2)	57(18.9)	19(6.3)
Elevated transaminase	43(14.2)	21(7.0)	22(7.3)
Elevated TB	39(12.9)	20(6.6)	19 (6.3)
Upper gastrointestinal bleeding	23(7.6)	1(0.3)	22 (7.3)
Hypoalbuminemia	40(13.2)	28(9.3)	12(4.0)
Ascites	53(17.5)	44(14.6)	9(3.0)
Fever	51(16.9)	48(15.9)	3(1.0)
Bacterial infection	12(4.0)	5(1.7)	7(2.3)
Abdominal pain	10(3.3)	6(2.0)	4(1.3)
Fatigue	28(9.3)	28 (9.3)	0
Anorexia	16 (5.3)	16(5.3)	0
Vomiting	7(2.3)	5(1.7)	2(0.7)
Diarrhea	16(5.3)	13 (4.3)	3(1.0)
Hand-Foot Syndrome	11(3.6)	9(3.0)	2(0.7)
Hypertension	13 (4.3)	8(2.6)	5(1.7)
Proteinuria	18(6.0)	14(4.6)	4(1.3)
Elevated serum creatinine	10(3.3)	5(1.7)	5(1.7)
Peptic ulcer	7(2.3)	6(2.0)	1(0.3)
Pulmonary embolism	6(2.0)	6(2.0)	0
Myocardial infarction	1(0.3)	0	1(0.3)
Aortic dissection	1(0.3)	0	1(0.3)
Diabetes	5(1.7)	2(0.7)	3(1.0)

(*Continued*)

Table 5 (Continued).

Adverse event	Any Grade n (%)	Grades 1–2 n (%)	Grades 3–4 n (%)
Colitis	4(1.3)	2(0.7)	2(0.7)
Myocarditis	5(1.7)	3 (1.0)	2(0.7)
Dermatitis	8(2.6)	4(1.3)	4 (1.3)
Pancreatitis	1(0.3)	0	1(0.3)
Nephritis	3(1.0)	1(0.3)	2(0.7)
Sjögren's syndrome	1(0.3)	0	1(0.3)
Systemic lupus erythematosus	1(0.3)	0	1(0.3)
Hepatitis	1(0.3)	0	1(0.3)
Pneumonia	3(1.0)	1(0.3)	2(0.7)
Adrenocortical insufficiency	6(2.0)	4(1.3)	2(0.7)
Encephalitis	1(0.3)	0	1(0.3)
Cerebral infarction	1(0.3)	0	1(0.3)
Tumor lysis syndrome	1(0.3)	0	1(0.3)
Anemia	11(3.6)	11(3.6)	0
Hypokalemia	10(3.3)	7(2.3)	3(1.0)
Rash	22(7.3)	13(4.3)	9(3.0)
Hypothyroidism	21(7.0)	21(7.0)	0
Pseudoaneurysm/hematoma	4(1.3)	4(1.3)	0

However, systemic therapies alone offer limited survival benefits. To prolong survival in patients with advanced u-HCC, locoregional intra-arterial treatment combined with systemic therapy might achieve higher survival benefits.

The rationale for combining locoregional HAIC with systemic treatment therapy lies in the highly heterogeneity of HCC, which lacks major molecular driver alterations and has a complex tumor microenvironment that monotherapy cannot adequately address. It has been reported that HAIC exerts a strong local tumor shrinkage effect with favorable objective response.[23] Oxaliplatin and fluorouracil may induce immunogenic cell death in cancer cells, resulting in immunostimulatory effects. Targeted drugs such as lenvatinib and sorafenib, as well as the anti-VEGF monoclonal antibody bevacizumab, can re-normalize tumor vasculature, which may facilitate antitumor immune cell infiltration.[24]

In this single-center retrospective study, encouraging survival outcomes were observed in a relatively large cohort of treatment-naive u-HCC patients receiving locoregional HAIC and systemic treatments, with a median PFS of 11.5 months and a median OS of 30.0 months. Of note, several centers have reported similar treatment strategies, with median PFS ranging from 4.4 to 13.9 months and median OS ranging from 11.3 to 26.3 months.[5,25–31] However, the number of patients enrolled in those studies was small. A meta-analysis of 1,019 pooled patients revealed an estimated median PFS of 9.7 months and median OS of 16.6 months,[32] which is comparable to our PFS result. As for the difference in median OS, the disparity may be partially attributed to patient characteristics and treatment allocation.

In univariable and multivariable analyses, AST, ALP, NLR, EHM, metabolic comorbidity, and combined systemic treatment modality were statistically independent risk factors associated with both PFS and OS. NLR is a marker of systemic inflammation and has been associated with patient survival and treatment response in several solid tumors.[33–36] Higher levels of AST and ALP, as well as the presence of EHM, are indicators of greater hepatic tumor burden and advanced clinical stage, and have been identified as independent factors associated with patient survival in other studies.[5,26,37]

In our analysis, metabolic comorbidity and combined ICIs and targeted/anti-VEGF therapy were independent favorable factors for both PFS and OS. A reasonable explanation is that these comorbidities are typically chronic metabolic abnormalities managed with statins, metformin, or aspirin, all of which have been shown to have favorable prognostic value in HCC patients.[38–40] ICIs together with targeted or anti-VEGF therapy have also been shown to be superior to ICIs or targeted therapy alone in HCC treatment in previous studies,[20,41,42] a finding consistent with our cohort.

The AEs observed in our study were common. An exception was the high occurrence of upper gastrointestinal bleeding (23 events) which has rarely been reported in other studies, suggesting that much attention should be paid to underlying portal hypertension associated with chronic liver disease and cirrhosis. A routine endoscopic evaluation for variceal screening and preventive management strategies such as ligation of esophageal varices and drug management, would be essential before anti-VEGF prescription.

Several limitations of our study should be acknowledged. First, this is a single-center retrospective study without randomization, and the lack of a control group is an inherent drawback. Additionally, potential selection bias and immortal time bias are unavoidable. Furthermore, the majority of HCC patients in our study were associated with chronic HBV infection (94.0%), which may limit the generalization of our findings on HCC patients with different etiologies. Moreover, different brands of ICIs and various targeted/anti-VEGF regimens were used in clinical practice, which may compromise the strength of our conclusions. Finally, the role of subsequent therapies after progression on HAIC plus ICIs and/or targeted therapy requires further exploration.

Conclusions

In conclusion, HAIC combined with systemic treatment comprising ICIs and targeted/anti-VEGF therapy is an effective and safe treatment modality for initially diagnosed u-HCC. Our preliminary results suggest that favorable survival outcomes can be expected in patients with AST $\leq$ 56.5 U/L, ALP $\leq$ 174.5 U/L, NLR $\leq$ 1.77, absence of EHM, presence of metabolic comorbidity, and treatment with HAIC plus ICIs and targeted/anti-VEGF therapy. These findings, however, require external and prospective validation.

Abbreviations

HCC, hepatocellular carcinoma; u-HCC, unresectable hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; CNLC, China Liver Cancer; EHM, extrahepatic metastasis; OS, overall survival; PFS, progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; PLT, platelet; PT, prothrombin time; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

Data Sharing Statement

The datasets generated during and/or analyzed through the current study are available from Maopei Chen on reasonable request.

Ethics Approval Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (B2025-265).

Informed Consent

This study has obtained IRB approval from Ethics Committee of Zhongshan Hospital, Fudan University (B2025-265) and the need for informed consent was waived because of the retrospective nature of the study. All patient-related information was anonymized and de-identified prior to data extraction and analysis. Strict protocols were implemented to ensure the confidentiality, privacy, and secure storage of all medical data. Patient records were accessible only to authorized research personnel, and all data were used solely for the purposes of this study, with no disclosure to third parties or unauthorized use.

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Disclosure

The authors declare that they have no conflict of interests.

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