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ORIGINAL RESEARCH

The Prognostic Value of CRP/Alb Ratio in Predicting Overall Survival for Hepatocellular Carcinoma Treated with Transcatheter Intra-Arterial Therapy Combined with Molecular-Targeted Agents and PD-1/PD-L1 Inhibitors

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Purpose: This study aimed to evaluate the prognostic value of C-reactive protein to albumin (CRP/Alb) ratio in hepatocellular carcinoma (HCC) treated with transcatheter intra-arterial therapy combined with molecular targeted agents (MTAs) and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors.

Methods: Medical records of 271 consecutive patients with HCC receiving this combination therapy in China between 2019 and 2023 were retrospectively analyzed. Prognostic factors for progression-free survival (PFS) and overall survival (OS) were identified using univariate and multivariate Cox regression analyses. The discriminatory capability of inflammation-based prognostic scores—including the CRP/Alb ratio, C-reactive protein and alpha-fetoprotein in immunotherapy (CRAFITY) score, modified Glasgow prognostic score (mGPS), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII)—was assessed using the area under the curve (AUC).

Results: A total of 133 patients met the inclusion criteria. The optimal cutoff value for the binary classification of CRP/Alb ratio in predicting OS, as determined using X-tile software, was 0.02. Multivariate analysis identified the CRP/Alb ratio (hazard ratio [HR] = 2.61, $p < 0.001$), tumor size (HR = 2.45, $p = 0.018$), and extrahepatic metastases (HR = 1.93, $p = 0.015$) as independent predictors of OS. For PFS, significant factors included Eastern Cooperative Oncology Group Performance Status (HR = 1.55, $p = 0.033$) and macrovascular invasion (HR = 1.48, $p = 0.046$). Patients with higher CRP/Alb ratios were more likely to experience fever and fatigue. The CRP/Alb ratio demonstrated significantly higher AUCs than PLR and SII at 24 months (all $p < 0.05$) and showed comparable AUCs to CRAFITY score and mGPS at 12, 24, and 36 months.

Conclusion: The CRP/Alb ratio is a valuable prognostic marker for predicting OS and treatment-related adverse events in HCC patients receiving transcatheter intra-arterial therapy combined with MTAs and PD-1/PD-L1 inhibitors. This ratio can be used as a simple and reliable biomarker for assessing prognosis and guiding patient selection in clinical practice.

Keywords: transarterial chemoembolization, hepatic artery infusion chemotherapy, targeted therapy, immunotherapy, inflammation, C-reactive protein

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and was the third leading cause of cancer-related mortality globally in 2020.[1] Over 70% of HCC patients forfeit the opportunity for curative treatment due to the advanced-stage disease at initial diagnosis.[2]

Transarterial chemoembolization (TACE) and hepatic artery infusion chemotherapy (HAIC) represent standard transcatheter intra-arterial therapies widely utilized in patients with unresectable HCC.[3] TACE remains the primary

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treatment for intermediate-stage HCC,[4] with its efficacy heavily rely on tumor burden.[5] HAIC can maintain elevated local concentrations of chemotherapeutic agents within tumors and has demonstrated efficacy for large, unresectable HCC.[6] It has been advocated as an alternative treatment for advanced-stage HCC in various Asian guidelines.[7–9] Recently, systemic therapies incorporating molecular targeted agents (MTAs) and immunotherapy have significantly reshaped the management of unresectable HCC, now commonly endorsed as first-line therapy for advanced disease.[4,10] Emerging evidence, including ongoing randomized controlled trials[11] and large-scale real-world study,[12] has shown promising outcomes from combining TACE with systemic therapy in HCC patients. Hence, there is an imperative to investigate reliable predictive markers for this combination regimen.

Inflammation plays a pivotal role in cancer development and progression.[13] C-reactive protein (CRP), an acute-phase protein predominantly synthesized in the liver, serves as a crucial marker of cancer-related systemic inflammation and may impede the effectiveness of immunotherapy.[14] Several inflammation-based prognostic scores, encompassing CRP and other markers, such as the CRP/albumin ratio, Glasgow Prognostic Score (GPS), and modified GPS (mGPS),[15–17] have demonstrated associations with survival outcomes in HCC. Additionally, the CRP and alpha-fetoprotein (AFP) in immunotherapy (CRAFITY) score has emerged as a novel and validated independent prognostic factor for HCC patients undergoing both immune monotherapy[18] and atezolizumab plus bevacizumab.[19] However, the predictive value of these scores was not extensively evaluated in HCC patients receiving transcatheter intra-arterial therapies combined with MTAs and ICIs.

Therefore, we aim to evaluate the prognostic significance of various inflammation-based scores in HCC patients treated with transcatheter intra-arterial therapies combined with MTAs and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors.

Materials and Methods

Study Design and Population

This retrospective study received approval from the institutional review board of Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, and the requirement for written informed consent was waived (approval number: 24/175-4455). We reviewed the medical records of 271 consecutive patients diagnosed with intermediate to advanced stage HCC, who underwent TACE or HAIC combined with MTA and PD-1/PD-L1 inhibitor between January 2019 and March 2023 at the National Cancer Center in China.

Inclusion criteria were as follows: ≥ 18 years old; histological or radiological diagnosis of HCC in accordance with the American Association for the Study of Liver Diseases (AASLD) criteria;[20] Barcelona Clinic Liver Cancer (BCLC) stage B or C; Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1; Child–Pugh score ≤ 7; received combination therapy of TACE or HAIC with MTA and PD-1/PD-L1 inhibitor during the same timeframe (the administration of systemic agents within 30 days before or after transcatheter intra-arterial therapy); at least one measurable target lesion that can be assessed by the modified Response Evaluation Criteria in Solid Tumors (mRECIST);[21] had laboratory test within 14 days before combination therapy. Patients with prior locoregional therapies, including surgery, ablation, TACE, or radiotherapy, were also included. Patients were excluded from this analysis for any of the following criteria: previously received any systemic therapy; concurrently undergoing other anticancer therapy; diagnosed with other primary malignancies; missing follow-up data.

Data Collection and Definition

Patient characteristics, including demographics, laboratory parameters such as AFP, CRP, albumin, neutrophil counts, lymphocyte counts, monocyte counts, and platelet counts, as well as ECOG PS, tumor size, and prior therapy, were extracted from electronic medical records.

The CRP/Alb ratio was calculated by dividing the CRP level (mg/dL) by the albumin level (g/L). For the CRAFITY score, patients with both elevated CRP (> 1.0 mg/dl) and AFP (> 100 ng/mL) were assigned a score of 2; those with only one of these abnormalities received a score of 1; while those with neither of these abnormalities were assigned a score of 0. For GPS, patients with both elevated CRP (> 1.0 mg/dl) and hypoalbuminemia (< 35 g/L) were allocated a score of 2; those with only one of these abnormalities received a score of 1; and those with neither were assigned a score of 0. Similarly, for mGPS, patients with both elevated CRP (> 1.0 mg/dl) and hypoalbuminemia (< 35 g/L) were assigned

a score of 2; those with elevated CRP only received a score of 1; and those with normal CRP levels and any albumin concentration were given a score of 0. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. The platelet-lymphocyte ratio (PLR) was determined by dividing the platelet count by the lymphocyte count. The monocyte-lymphocyte ratio (MLR) was calculated by dividing the monocyte count by the lymphocyte count. The systemic immune-inflammation index (SII) was derived from platelet × neutrophil/lymphocyte. The prognostic nutritional index (PNI) was calculated by albumin + 5 × lymphocyte.

Transcatheter Intra-Arterial Therapy

Transcatheter intra-arterial therapies were conducted by interventional radiologists with over a decade of clinical experience, utilizing digital subtraction angiography for guidance. Vascular access was established via the right femoral artery using the Seldinger technique and a 5-French vessel access kit (Radiofocus; Terumo) under local anesthesia. Angiographic evaluation of the celiac trunk and superior mesenteric artery was performed with a 5-French catheter.

For the TACE procedure, a 2.4-French microcatheter was advanced to super-selectively catheterize the tumor-feeding arteries. An emulsion consisting of lipiodol (2–20 mL) and chemotherapeutic agents (anthracycline or platinum, 10–50 mg/m²) was administered through the microcatheter. Subsequently, absorbable gelatin sponge particles were deployed to embolize the tumor-feeding arteries, achieving arterial flow stasis. Repeat TACE sessions were performed as on-demand based on follow-up imaging identifying new or residual tumors.

For HAIC, a 2.7-French microcatheter was selectively placed in the tumor-feeding artery. In cases where tumors received additional blood supply from extrahepatic arteries, the microcatheter was positioned in the main feeding artery, and the branch arteries were embolized with blank microspheres. In cases where a short access pathway from the intrahepatic arteries to the gastroduodenal artery existed, potentially causing the reflux of chemotherapy agents into the stomach and duodenum, coils were used to embolize this pathway. The external catheter segment was wrapped in sterile gauze and secured to the thigh with rubberized fabric and a bandage. Following this, patients were transferred to the ward for chemotherapeutic infusion: oxaliplatin (85 mg/m^2) over 2–4 hours, leucovorin (400 mg/m^2) over 2 hours, fluorouracil (400 mg/m^2) over 1 hour, and an extended infusion of fluorouracil (2400 mg/m^2) over 46 hours. HAIC was repeated every 4–6 weeks, with a maximum of six cycles administered.

Systemic Therapy

Several PD-1/PD-L1 inhibitors (sintilimab, toripalimab, atezolizumab, camrelizumab, tislelizumab, pembrolizumab, and nivolumab) were utilized based on guidelines and availability in China (Supplementary Table 1). All PD-1/PD-L1 inhibitors were administered at their standard doses and frequencies. Various MTAs (tyrosine kinase inhibitors and anti-vascular endothelial growth factor), including lenvatinib, sorafenib, regorafenib, apatinib, and bevacizumab, were administered at their standard doses (Supplementary Table 1). PD-1/PD-L1 inhibitors and oral MTAs were given within 30 days before or after the transcatheter intra-arterial therapies. Bevacizumab administered concurrently with PD-1/PD-L1 inhibitors. Systemic therapy was maintained until disease progression or unacceptable toxicities occurred.

Clinical Outcomes and Follow-Up

The Best Overall Response (BOR) was evaluated using the mRECIST. The Objective response rate (ORR) comprised complete response (CR) and partial response (PR). The disease control rate (DCR) encompassed CR, PR, and stable disease (SD). Progression-free survival (PFS) and overall survival (OS) were calculated from the onset of combination therapy until each event or last follow-up. Patients were routinely followed with CT or MRI: at 1-month after intra-arterial therapies, every 2–3 months for the initial 6 months, and subsequently every 3–6 months. Follow-up was conducted via telephone interviews (May 1, 2024) or during the last hospital visit if a telephone interview was unfeasible. The severity of treatment-related adverse events (TRAEs) was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v 5.0).

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on their distribution. Comparisons between groups were conducted using either the *t*-test or Mann–Whitney *U*-test, as appropriate. Categorical variables were expressed as counts and percentages and analyzed using the χ^2 test or Fisher's exact test, based on applicability. The optimal cutoff value for continuous prognostic scores used to stratify OS was determined with X-tile software,[22] a validated tool for optimizing biomarker assessment and outcome-based cutoff values. Kaplan–Meier survival analyses were performed to estimate survival probabilities, with group comparisons assessed using the Log rank test. Univariate and multivariate Cox proportional hazards models were used to identify independent predictors of OS and PFS, with results expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). To evaluate the predictive performance of the CRP/Alb ratio, time-dependent receiver operating characteristic (ROC) curve analysis was conducted, and the area under the ROC curve (AUC) was compared with other inflammation-based scores at various time points. All statistical analyses were performed using R software version 4.2.3 (R Foundation for Statistical Computing; http://www.R-project.org). A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 133 patients were included in the study (Figure 1). The mean age was 56.02 ± 11.02 years, and the majority of patients were male (n = 118, 88.72%). Over half of the patients (n = 74, 55.64%) had BCLC stage C disease. Most had well-preserved liver function, as indicated by Child–Pugh class A status (n = 113, 84.96%), and a high prevalence of hepatitis B virus infection was observed (n = 113, 84.96%). Macrovascular invasion was present in 42.86% of patients (n = 57), while 24.81% (n = 33) had extrahepatic metastases. Transcatheter intra-arterial therapy was performed in 88 patients (66.17%) via TACE and in 45 patients (33.83%) via HAIC. The median number of TACE and HAIC sessions was 3.00 (IQR 2.00–4.00) and 3.00 (IQR 2.00–5.00), respectively. Patients received a median of 8.00 cycles of PD-1/PD-L1 inhibitors (IQR 4.00–12.00). The median CRP/Alb ratio was 0.02 (IQR 0.00–0.05). Two optimal cutoff values for the CRP/Alb ratio were identified: 0.02 for binary classification and 0.01 and 0.02 for trichotomous classification. Additional optimal cutoff values for other inflammation-based scores were determined as follows: MLR (0.17), PLR (86.7), PNI

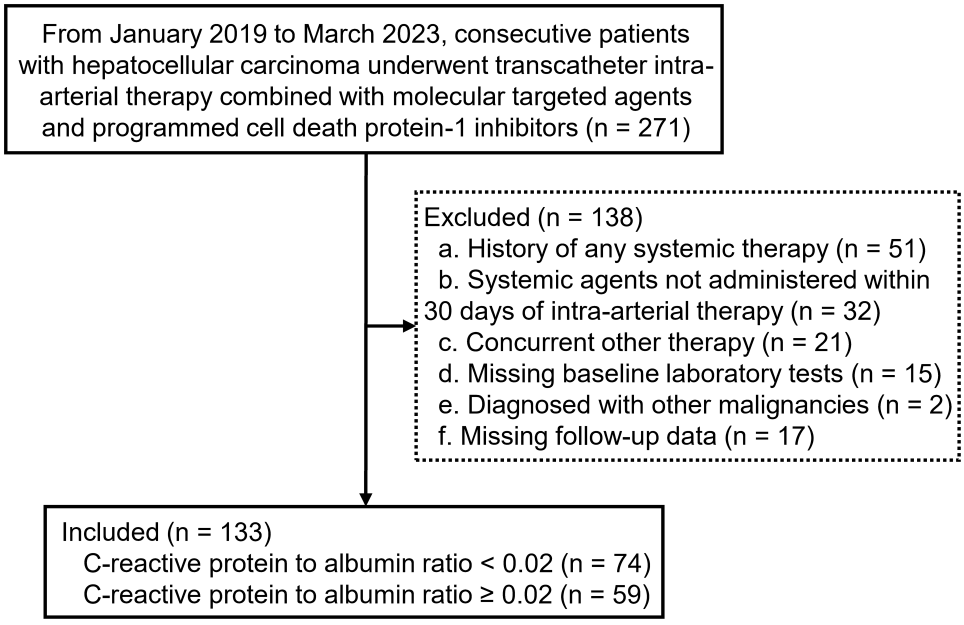

Figure 1 Flowchart of the study.

Table 1 Patient Characteristics

Characteristics	Total (n = 133)	CRP/Alb < 0.02 (n = 74)	CRP/Alb ≥ 0.02 (n = 59)	*P*
Age, Mean ± SD	56.02 ± 11.02	57.11 ± 11.20	54.64 ± 10.72	0.201
Sex, n (%)				0.361
Female	15 (11.28)	10 (13.51)	5 (8.47)	
Male	118 (88.72)	64 (86.49)	54 (91.53)	
ECOG PS, n (%)				0.301
0	94 (70.68)	55 (74.32)	39 (66.10)	
1	39 (29.32)	19 (25.68)	20 (33.90)	
BCLC stage, n (%)				0.143
B	59 (44.36)	37 (50.00)	22 (37.29)	
C	74 (55.64)	37 (50.00)	37 (62.71)	
Child–Pugh, n (%)				0.582
A	113 (84.96)	64 (86.49)	49 (83.05)	
B7	20 (15.04)	10 (13.51)	10 (16.95)	
Etiology, n (%)				0.661
Hepatitis B	113 (84.96)	62 (83.78)	51 (86.44)	
Hepatitis C	2 (1.50)	2 (2.70)	0 (0.00)	
None	18 (13.53)	10 (13.51)	8 (13.56)	
Largest Tumor size (cm), M (IQR)	7.50 (4.60, 11.60)	5.70 (3.58, 8.57)	10.60 (7.45, 13.05)	<0.001
Tumor number, n (%)				0.020
< 3	53 (39.85)	36 (48.65)	17 (28.81)	
≥ 3	80 (60.15)	38 (51.35)	42 (71.19)	
Macrovascular Invasion, n (%)				0.018
No	76 (57.14)	49 (66.22)	27 (45.76)	
Yes	57 (42.86)	25 (33.78)	32 (54.24)	
Extrahepatic Metastases, n (%)				0.796
No	100 (75.19)	55 (74.32)	45 (76.27)	
Yes	33 (24.81)	19 (25.68)	14 (23.73)	
Cirrhosis, n (%)				0.627
No	64 (48.12)	37 (50.00)	27 (45.76)	
Yes	69 (51.88)	37 (50.00)	32 (54.24)	
AFP (ng/mL), n (%)				0.273
< 100	52 (39.10)	32 (43.24)	20 (33.90)	
≥ 100	81 (60.90)	42 (56.76)	39 (66.10)	
CRP (mg/dL), M (IQR)	0.71 (0.18, 2.21)	0.21 (0.08, 0.44)	2.48 (1.50, 3.82)	<0.001
Albumin (g/L), M (IQR)	40.60 (37.40, 43.50)	41.60 (38.25, 43.88)	40.20 (36.05, 42.90)	0.026
PNI, M (IQR)	48.55 (43.75, 52.25)	49.08 (44.60, 53.01)	47.55 (43.33, 51.85)	0.164
MLR, M (IQR)	0.27 (0.19, 0.37)	0.24 (0.18, 0.31)	0.29 (0.22, 0.43)	0.002
PLR, M (IQR)	121.21 (82.88, 154.63)	108.05 (77.42, 141.10)	131.27 (94.28, 179.99)	0.014
SII, M (IQR)	442.32 (229.33, 679.26)	325.49 (202.34, 545.98)	581.87 (308.32, 849.96)	<0.001
NLR, M (IQR)	2.42 (1.68, 3.48)	2.09 (1.52, 3.54)	2.85 (2.02, 3.47)	0.080
CRP/Alb ratio, M (IQR)	0.02 (0.00, 0.05)	0.01 (0.00, 0.01)	0.06 (0.04, 0.10)	<0.001
CRAFITY score, n (%)				<0.001
0	35 (26.32)	32 (43.24)	3 (5.08)	
1	65 (48.87)	42 (56.76)	23 (38.98)	
2	33 (24.81)	0 (0.00)	33 (55.93)	
Targeted Therapy, n (%)				0.736
Lenvatinib	72 (54.14)	38 (51.35)	34 (57.63)	
Bevacizumab	38 (28.57)	23 (31.08)	15 (25.42)	
Others	23 (17.29)	13 (17.57)	10 (16.95)	

(*Continued*)

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Table 1 (Continued).

Characteristics	Total (n = 133)	CRP/Alb < 0.02 (n = 74)	CRP/Alb ≥ 0.02 (n = 59)	*P*
Immunotherapy, n (%)				0.042
Sintilimab	36 (27.07)	18 (24.32)	18 (30.51)	
Toripalimab	26 (19.55)	8 (10.81)	18 (30.51)	
Atezolizumab	23 (17.29)	15 (20.27)	8 (13.56)	
Camrelizumab	19 (14.29)	15 (20.27)	4 (6.78)	
Tislelizumab	15 (11.28)	9 (12.16)	6 (10.17)	
Pembrolizumab	11 (8.27)	7 (9.46)	4 (6.78)	
Nivolumab	3 (2.26)	2 (2.70)	1 (1.69)	
Intra-arterial Therapy, n (%)				0.452
TACE	88 (66.17)	51 (68.92)	37 (62.71)	
HAIC	45 (33.83)	23 (31.08)	22 (37.29)	
Prior Therapy, n (%)				0.002
No	95 (71.43)	45 (60.81)	50 (84.75)	
Yes	38 (28.57)	29 (39.19)	9 (15.25)	
Immunotherapy Cycles, M (IQR)	8.00 (4.00, 12.00)	8.00 (4.00, 12.75)	7.00 (4.00, 10.50)	0.217

Abbreviations: SD, standard deviation; M, Median; IQR, Interquartile Range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; CRP, C-reactive protein; PNI, prognostic nutritional index; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; CRP/Alb, C-reactive protein/albumin; CRAFITY, C-reactive protein and alpha-fetoprotein in immunotherapy score; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy.

(53.4), and SII (546.4). Approximately half of the patients (n = 65, 48.87%) were assigned to the CRAFITY 1 score group. Patient characteristics stratified by the binary CRP/Alb ratio are detailed in Table 1. Patients with an elevated CRP/Alb ratio (≥ 0.02) exhibited significantly larger tumor sizes, multiple tumors, and a higher incidence of macrovascular invasion compared to those with a lower CRP/Alb ratio (all p <0.05).

Clinical Outcomes and Prognostic Factors

The median follow-up duration was 32.67 months (95% CI 29.57–35.76). Patients in the high CRP/Alb ratio group demonstrated significantly worse OS compared to those in the low CRP/Alb ratio group, whether classified into two or three groups (all $p < 0.001$; Figure 2A and B). The median OS was 19.37 months (95% CI 17.23–28.97) for patients with a CRP/Alb ratio ≥ 0.02, compared to 46.50 months (95% CI 34.60–NA) for those with a CRP/Alb ratio < 0.02. Among patients with CRAFITY scores of 0, 1, and 2, the median OS was not evaluable (NE), 32.33 months (95% CI 26.47–NA), and 20.30 months (95% CI 14.37–28.97), respectively, with significant differences among groups ($p < 0.001$; Figure 2C). PFS showed no statistically significant differences in the analysis of the entire patient population. The median PFS was 9.37 months for patients with a CRP/Alb ratio ≥ 0.02 and 10.57 months for those with a CRP/Alb ratio < 0.02 ($p = 0.191$). For patients with CRAFITY scores of 0, 1, and 2, the median PFS was 10.00, 10.60, and 9.66 months, respectively ($p = 0.397$).

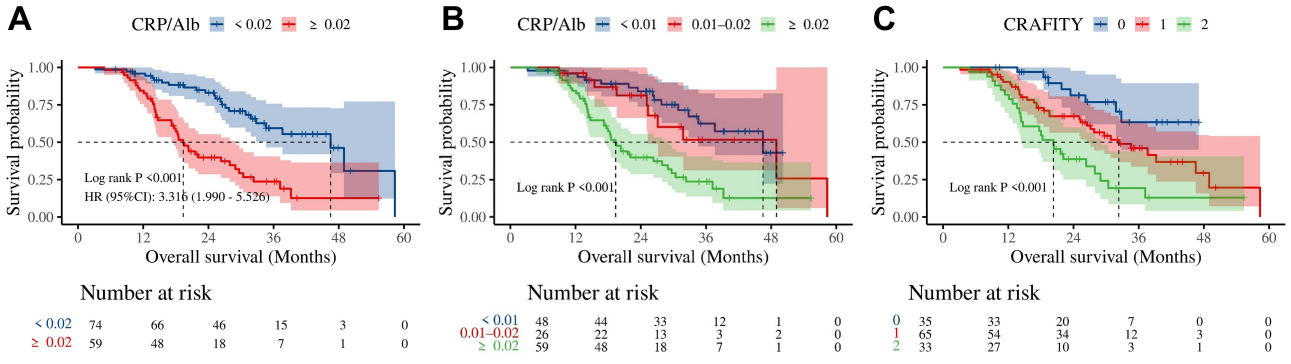

Figure 2 Kaplan–Meier curves for overall survival based on: (**A**) binary classifications of the C-reactive protein/albumin (CRP/Alb) ratio, (**B**) trichotomous classifications of the CRP/Alb ratio, and (**C**) the C-reactive protein and alpha-fetoprotein in the immunotherapy (CRAFITY) score.

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Univariate analysis identified several factors significantly associated with worse OS, including BCLC stage C, Child–Pugh class B7, tumor size ≥ 5 cm, macrovascular invasion, extrahepatic metastases, CRP ≥ 1 mg/dL, PLR ≥ 86.7, SII ≥ 546.4, CRP/Alb ratio ≥ 0.02, CRAFITY scores of 1 or 2, GPS of 1 or 2, and mGPS of 1 or 2 (all $p < 0.05$; Table 2). To avoid collinearity bias due to the correlations among inflammation-based scores (PLR, SII, GPS, mGPS, and CRAFITY

Table 2 Prognostic Factors for Progression-Free Survival and Overall Survival

Variables	Progression-Free Survival				Overall Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years), ≥ 60	1.05 (0.70 – 1.58)	0.815			0.79 (0.46 – 1.34)	0.375		
Sex, Female	0.75 (0.38 – 1.49)	0.412			1.31 (0.62 – 2.76)	0.476		
ECOG PS, 1	1.62 (1.08 – 2.42)	0.019	1.55 (1.04 – 2.33)	0.033	1.52 (0.92 – 2.52)	0.103		
BCLC Stage, C	1.26 (0.85 – 1.87)	0.254			1.87 (1.10 – 3.17)	0.021	1.05 (0.57 – 1.94)	0.877
Child–Pugh, B7	1.07 (0.65 – 1.79)	0.784			1.82 (1.01 – 3.31)	0.049	1.13 (0.59 – 2.15)	0.709
Etiology								
None	1.00 (Reference)				1.00 (Reference)			
Hepatitis B	1.89 (0.97 – 3.66)	0.060			0.93 (0.46 – 1.89)	0.845		
Hepatitis C	3.02 (0.38 – 23.99)	0.295			0.00 (0.00 – Inf)	0.997		
Tumor size (cm), ≥5	1.00 (0.65 – 1.53)	0.988			3.35 (1.65 – 6.80)	<0.001	2.45 (1.16 – 5.14)	0.018
Tumor Number, ≥ 3	1.14 (0.77 – 1.70)	0.515			1.66 (0.99 – 2.77)	0.053		
Macrovascular Invasion, Yes	1.54 (1.05 – 2.25)	0.027	1.48 (1.01 – 2.17)	0.046	2.21 (1.35 – 3.63)	0.002	1.66 (0.95 – 2.89)	0.073
Extrahepatic Metastases, Yes	1.43 (0.93 – 2.21)	0.101			1.72 (1.03 – 2.86)	0.037	1.93 (1.14 – 3.28)	0.015
Cirrhosis, Yes	1.47 (1.01 – 2.17)	0.050			0.94 (0.58 – 1.53)	0.808		
AFP (ng/mL), ≥ 100	0.93 (0.63 – 1.38)	0.718			1.66 (0.97 – 2.85)	0.064		
CRP (mg/dl), ≥ 1	1.15 (0.78 – 1.69)	0.483			3.10 (1.83 – 5.24)	<0.001		
Albumin (g/L), ≥ 35	0.98 (0.56 – 1.70)	0.937			1.17 (0.56 – 2.45)	0.684		
PNI, ≥ 53.4	1.12 (0.67 – 1.86)	0.671			2.09 (0.99 – 4.38)	0.052		
MLR, ≥ 0.17	1.16 (0.64 – 2.08)	0.627			1.60 (0.73 – 3.52)	0.238		
PLR, ≥ 86.7	1.49 (0.95 – 2.33)	0.080			2.28 (1.19 – 4.36)	0.013		
SII, ≥ 546.4	1.10 (0.74 – 1.64)	0.628			2.08 (1.27 – 3.39)	0.003		
NLR, ≥ 3	1.34 (0.90 – 1.98)	0.150			1.20 (0.73 – 1.98)	0.474		
CRP/Alb ratio								
Binary, ≥ 0.02	1.29 (0.88 – 1.89)	0.194			3.32 (1.99 – 5.53)	<0.001	2.61 (1.52 – 4.46)	<0.001
Trichotomous								
< 0.01	1.00 (Reference)				1.00 (Reference)			
0.01–0.02	1.03 (0.57 – 1.86)	0.922			1.37 (0.60 – 3.15)	0.134		
≥ 0.02	1.30 (0.85 – 1.98)	0.223			3.70 (2.03 – 6.73)	<0.001		
CRAFITY score								
0	1.00 (Reference)				1.00 (Reference)			
1	0.79 (0.48 – 1.28)	0.337			2.38 (1.10 – 5.18)	0.028		
2	1.05 (0.61 – 1.80)	0.375			4.96 (2.22 – 11.05)	<0.001		
GPS								
0	1.00 (Reference)				1.00 (Reference)			
1	1.11 (0.75 – 1.66)	0.595			2.26 (1.35 – 3.79)	0.002		
2	1.17 (0.55 – 2.46)	0.683			2.45 (1.01 – 5.95)	0.048		
mGPS								
0	1.00 (Reference)				1.00 (Reference)			
1	1.14 (0.76 – 1.72)	0.521			3.06 (1.82 – 5.13)	<0.001		
2	1.17 (0.56 – 2.45)	0.680			2.59 (1.07 – 6.27)	0.035		

(*Continued*)

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Table 2 (Continued).

Variables	Progression-Free Survival				Overall Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Targeted Therapy								
Bevacizumab	1.00 (Reference)				1.00 (Reference)			
Lenvatinib	1.55 (0.82 – 2.91)	0.176			1.55 (0.82 – 2.91)	0.176		
Others	1.64 (0.78 – 3.45)	0.196			1.64 (0.78 – 3.45)	0.196		
Immunotherapy								
Camrelizumab	1.00 (Reference)				1.00 (Reference)			
Sintilimab	1.03 (0.56 – 1.90)	0.912			1.74 (0.77 – 3.93)	0.183		
Atezolizumab	1.10 (0.55 – 2.19)	0.783			1.43 (0.56 – 3.64)	0.450		
Toripalimab	0.81 (0.43 – 1.54)	0.526			1.60 (0.69 – 3.73)	0.274		
Others	0.89 (0.45 – 1.75)	0.728			1.10 (0.42 – 2.87)	0.841		
HAIC, Yes	1.11 (0.74 – 1.65)	0.619			1.48 (0.89 – 2.46)	0.128		
Prior Therapy, Yes	1.38 (0.91 – 2.09)	0.135			0.78 (0.44 – 1.37)	0.382		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; CRP, C-reactive protein; PNI, prognostic nutritional index; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; CRP/Alb, C-reactive protein/albumin; CRAFITY, C-reactive protein and alpha-fetoprotein in immunotherapy score; GPS, Glasgow prognostic score; mGPS, modified GPS; HAIC, hepatic artery infusion chemotherapy.

score), only the binary CRP/Alb ratio classification was included in the multivariate analysis. Multivariate analysis revealed that CRP/Alb ratio ≥ 0.02 (HR = 2.61; $p < 0.001$), tumor size ≥ 5 cm (HR = 2.45; $p = 0.018$), and extrahepatic metastases (HR = 1.93; $p = 0.015$) were independent prognostic factors for worse OS. For PFS, multivariate analysis identified ECOG PS (HR = 1.55; $p = 0.033$) and macrovascular invasion (HR = 1.48; $p = 0.046$) as independent prognostic factors (Table 2).

Comparison of Prognostic Scores

ROC curves were generated to evaluate OS at 12, 24, and 36 months of follow-up. The ROC curves for inflammation-based scoring systems with AUC values greater than 0.5 are presented in Figure 3. Both the CRP/Alb ratio and the CRAFITY score demonstrated strong prognostic value for OS. In predicting 12-month OS (Figure 3A), the CRAFITY score showed a slightly higher AUC (0.703) than the trichotomous CRP/Alb ratio (AUC: 0.651); however, this difference was not statistically significant ($p = 0.285$). For 24-month OS, the CRP/Alb ratio exhibited the highest AUC, with the

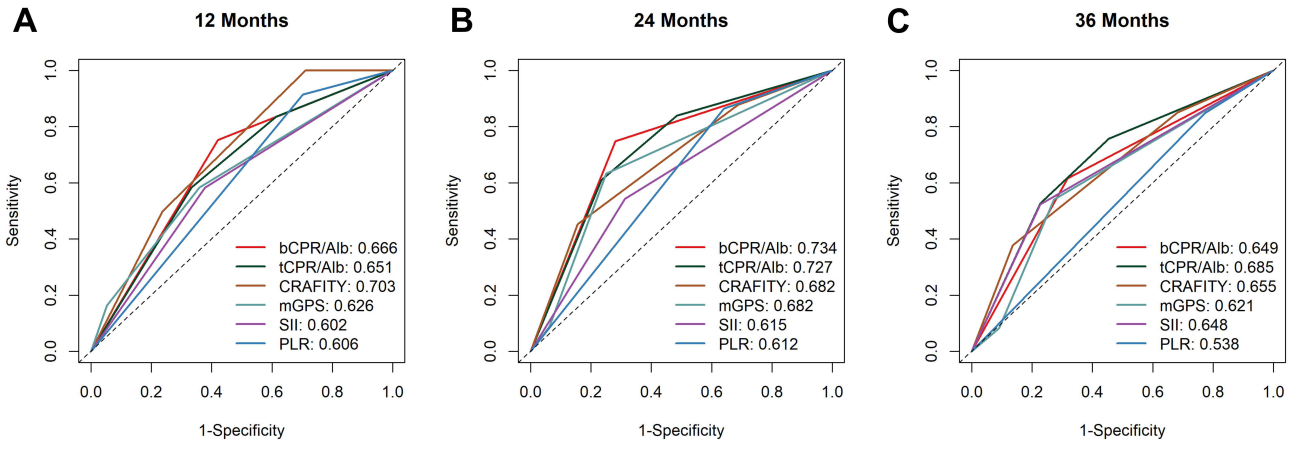

Figure 3 Areas under the time-dependent receiver operating curves for predicting overall survival using six inflammation-based prognostic scores at: (**A**) 12 months, (**B**) 24 months, and (**C**) 36 months. Abbreviations: bCRP/Alb binary classification of C-reactive protein/albumin (CRP/Alb) ratio; tCRP/Alb trichotomous classification of CRP/Alb ratio; CRAFITY C-reactive protein and alpha-fetoprotein in immunotherapy score; mGPS modified Glasgow prognostic score; SII systemic immune-inflammation index; PLR platelet-lymphocyte ratio.

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binary classification achieving an AUC of 0.734 and the trichotomous classification an AUC of 0.727 (Figure 3B). Notably, the binary CRP/Alb ratio demonstrated significant statistical differences compared to the SII (AUC: 0.615, $p = 0.039$; Supplementary Table 2) and PLR (AUC: 0.612, $p = 0.038$; Supplementary Table 2). For 36-month OS prediction (Figure 3C), the trichotomous CRP/Alb ratio reached the highest AUC value of 0.685.

Subgroup Analyses

HCC patients were stratified into subgroups for detailed analysis. A CRP/Alb ratio ≥ 0.02 consistently correlated with worse OS across several subgroups, including patients with BCLC stage B ($p = 0.003$) and stage C ($p < 0.001$), AFP < 100 ng/mL ($p < 0.001$) and AFP ≥ 100 ng/mL ($p < 0.001$), those treated with TACE ($p < 0.001$), lenvatinib ($p < 0.001$), and sintilimab ($p = 0.006$), as well as toripalimab ($p = 0.004$) (Supplementary Figures 1A–E, 2A, and 3A C). However, the association was not statistically significant in the HAIC ($p = 0.074$) or bevacizumab ($p = 0.082$) subgroups (Supplementary Figures 1F and 2C). For PFS, a significant relationship with the CRP/Alb ratio was observed only in the lenvatinib subgroup ($p = 0.009$; Supplementary Figure 2B). No significant associations were found in the bevacizumab ($p = 0.984$), sintilimab ($p = 0.098$), or toripalimab ($p = 0.124$) subgroups (Supplementary Figures 2D, and 3B D).

Tumor Response

The BOR is summarized in Supplementary Table 3. CR, PR, SD, and PD were observed in 10 (7.52%), 80 (60.15%), 37 (27.82%), and 6 (4.51%) patients, respectively. The ORR and DCR for all patients were 67.67% and 95.49%, respectively. In the low CRP/Alb ratio group, the ORR was 67.57%, while the high CRP/Alb ratio group had a slightly higher ORR of 67.80% ($p = 0.978$). The DCR was 91.89% for the low CRP/Alb ratio group and 100.0% for the high CRP/Alb ratio group ($p = 0.069$).

Safety Profiles

TRAEs with an incidence of 10% or greater are summarized in Table 3. All TRAEs were manageable, and no treatment-related deaths occurred during the study period. Patients with a higher CRP/Alb ratio were more likely to experience fever and fatigue compared to those with a lower CRP/Alb ratio ($p = 0.014$ and $p = 0.030$, respectively). The most common grade 3 or higher TRAEs were hypertension, observed in 10 patients (7.52%). No significant correlation was found between grade 3 or higher TRAEs and the CRP/Alb ratio. Patients who experienced grade 3 or higher TRAEs underwent dose adjustments or treatment discontinuation.

Table 3 Treatment-Related Adverse Events Stratified by the Binary CRP/Alb Ratio

Adverse Events	Total (n = 133)	CRP/Alb < 0.02 (n = 74)	CRP/Alb ≥ 0.02 (n = 59)	P
Abdominal pain				
Any grade	69 (51.88)	43 (58.11)	26 (44.07)	0.107
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Nausea				
Any grade	57 (42.86)	37 (50.00)	20 (33.90)	0.062
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Decreased appetite				
Any grade	53 (39.85)	28 (37.84)	25 (42.37)	0.596
Grade ≥ 3	1 (0.75)	0 (0.00)	1 (1.69)	0.444
Fever				
Any grade	50 (37.59)	21 (28.38)	29 (49.15)	0.014
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–

(*Continued*)

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Table 3 (Continued).

Adverse Events	Total (n = 133)	CRP/Alb < 0.02 (n = 74)	CRP/Alb ≥ 0.02 (n = 59)	*P*
Proteinuria				
Any grade	43 (32.33)	26 (35.14)	17 (28.81)	0.439
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Rash				
Any grade	42 (31.58)	19 (25.68)	23 (38.98)	0.101
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Diarrhea				
Any grade	41 (30.83)	22 (29.73)	19 (32.20)	0.759
Grade ≥ 3	1 (0.75)	1 (1.35)	0 (0.00)	1.000
Leukocytopenia				
Any grade	40 (30.08)	18 (24.32)	22 (37.29)	0.105
Grade ≥ 3	3 (2.26)	2 (2.70)	1 (1.69)	1.000
Hypertension				
Any grade	39 (29.32)	22 (29.73)	17 (28.81)	0.908
Grade ≥ 3	10 (7.52)	5 (6.76)	5 (8.57)	0.966
Elevated AST				
Any grade	39 (29.32)	26 (35.14)	13 (22.03)	0.099
Grade ≥ 3	5 (3.76)	2 (2.70)	3 (5.08)	0.796
Vomiting				
Any grade	38 (28.57)	22 (29.73)	16 (27.12)	0.741
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Fatigue				
Any grade	37 (27.82)	15 (20.27)	22 (37.29)	0.030
Grade ≥ 3	1 (0.75)	0 (0.00)	1 (1.69)	0.444
Thrombocytopenia				
Any grade	36 (27.07)	24 (32.43)	12 (20.34)	0.119
Grade ≥ 3	1 (0.75)	0 (0.00)	1 (1.69)	0.444
Decreased albumin				
Any grade	33 (24.81)	16 (21.62)	17 (28.81)	0.340
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Elevated ALT				
Any grade	32 (24.06)	20 (27.03)	12 (20.34)	0.370
Grade ≥ 3	2 (1.50)	1 (1.35)	1 (1.69)	1.000
Hand-foot syndrome				
Any grade	32 (24.06)	17 (22.97)	15 (25.42)	0.743
Grade ≥ 3	2 (1.50)	1 (1.35)	1 (1.69)	1.000
Hypothyroidism				
Any grade	28 (21.05)	16 (21.62)	12 (20.34)	0.857
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–
Elevated TBIL				
Any grade	21 (15.79)	13 (17.57)	8 (13.56)	0.529
Grade ≥ 3	0 (0.00)	0 (0.00)	0 (0.00)	–

Note: Data were presented as n (%).
Abbreviations: CRP/Alb, C-reactive protein/albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin.

Discussion

This study highlights the significant prognostic value of inflammation-based scores, particularly those incorporating CRP, in patients with HCC undergoing treatment with TACE or HAIC combined with MTAs and PD-1/PD-L1 inhibitors. Emerging evidence supports this combination therapy as a promising option for managing unresectable HCC, with

multiple ongoing clinical trials.[23] Consequently, identifying reliable biomarkers for predicting outcomes in this regimen is critical. In the univariate analysis, several inflammation-based markers, including CRP, CRP/Alb ratio, CRAFITY score, GPS, mGPS, PLR, and SII, demonstrated significant associations with OS. Among these, the CRP/Alb ratio offered superior predictive accuracy and discrimination for 24-month OS (AUC: 0.734). Its performance was statistically significant compared to PLR and SII (all $p < 0.05$). Furthermore, patients with an elevated CRP/Alb ratio were more likely to experience TRAEs, such as fever and fatigue. These findings suggest that inflammation-based scores, particularly the CRP/Alb ratio, may serve as practical and effective tools for predicting OS and the risk of TRAEs in patients receiving this combination therapy.

Systemic inflammatory responses involve various cytokines that can promote tumor growth and metastasis, playing a critical role in the poor prognosis of patients with malignancies. CRP, an acute-phase protein synthesized by hepatocytes, is primarily elevated in response to pro-inflammatory cytokines, particularly interleukin-6.[24] Elevated CRP levels have been independently associated with poor OS in patients with HCC.[16] Furthermore, CRP exhibits significant immunosuppressive properties in cancer. For instance, in melanoma, CRP has been shown to inhibit the proliferation of activated CD4+ and CD8+ T cells, suppress co-stimulatory signaling on dendritic cells, and impair the expansion of MART-1 antigen-specific CD8+ T cells.[25] Additionally, CRP can stimulate the expansion of myeloid-derived suppressor cells, further dampening anti-tumor immune responses and facilitating immune evasion by cancer cells.[26] In HCC, higher baseline CRP levels have been shown to predict unfavorable immunotherapy outcomes,[27,28] emphasizing its potential as a prognostic indicator. Elevated CRP levels are also associated with systemic effects such as increased tissue metabolism and protein loss, contributing to poor nutritional status and higher mortality risk.[29] Serum albumin, a well-established marker of nutritional status and disease prognosis, provides complementary insights. Its degradation and turnover rates are significantly accelerated in aggressive tumor subtypes.[30] This is particularly relevant in HCC, where underlying cirrhosis is common, and the combined effects of cirrhosis and tumor-induced hepatic dysfunction exacerbate nutritional deficiencies. Notably, serum albumin levels have been correlated with immunotherapy outcomes across various cancers.[31,32] A large-scale study based on the Memorial Sloan Kettering Cancer Center database demonstrated a dose-dependent relationship between baseline albumin levels and improved immunotherapy efficacy,[32] reinforcing the prognostic significance of this marker. These findings support the exploration of the CRP/Alb ratio as a potential prognostic biomarker for HCC patients undergoing immunotherapy.

In fact, the CRP/Alb ratio has emerged as a novel prognostic biomarker for survival in patients with HCC undergoing surgery,[33] locoregional therapy,[34] targeted therapy,[35] and immunotherapy,[31] with the optimal cutoff value ranging from 0.004 to 0.028. However, its prognostic utility in HCC patients receiving locoregional therapies combined with MTAs and immunotherapy remains underexplored. Currently, MTAs such as lenvatinib, sorafenib, and donafenib are common options for molecular-targeted monotherapy in HCC, with reported ORRs of less than 25%.[36] Similarly, immunotherapy as a monotherapy for HCC demonstrates limited efficacy, with ORRs of approximately 20%.[37] In contrast, combining targeted therapy with immunotherapy has shown improved outcomes, with ORRs reaching 30%.[37] Notably, the integration of transcatheter intra-arterial therapy with MTAs and immunotherapy has exhibited significantly higher efficacy, with reported ORRs reaching 70%,[38] as observed in our study with an ORR of 67.67%. Therefore, identifying robust prognostic biomarkers for this combined regimen is critical to optimize patient management. In this study, we compared the prognostic value of several inflammation-based markers in HCC patients treated with the combination regimen. Among these, the CRP/Alb ratio outperformed commonly used indicators, such as the GPS and mGPS, in predicting OS, demonstrating higher AUC values and HRs in univariate Cox regression analyses. This superior performance may be attributed to the CRP/Alb ratio's continuous variable nature, which better captures the dose-dependent relationship between inflammation and survival outcomes. These findings are consistent with prior studies comparing these markers in HCC.[17,34] Additionally, the CRAFITY score, which stratifies patients based on AFP and CRP levels, showed prognostic performance comparable to the trichotomous CRP/Alb ratio in our cohort (AUC: 0.655–0.703 vs 0.651–0.727; all $p > 0.05$). The CRAFITY score, a recently developed and validated tool based on large cohort data, has shown strong prognostic value in HCC patients treated with immunotherapy-based systemic therapy.[18] Its predictive performance has been demonstrated in HCC patients receiving atezolizumab plus bevacizumab,[18,19] as well as in those undergoing intra-arterial therapy combined with immunotherapy,[39] with reported AUCs ranging from 0.62 to 0.71.

Similar AUC ranges (0.655–0.703) were observed in our study. Importantly, the binary CRP/Alb ratio achieved the highest AUC (0.734) for predicting 24-month OS in our study and demonstrated the strongest association with OS in multivariate Cox regression analysis (HR: 2.61; 95% CI 1.52–4.46). Subgroup analyses further confirmed the prognostic value of the CRP/Alb ratio across patient subgroups stratified by BCLC stage, AFP levels, and treatment modalities, consistently associating higher CRP/Alb ratios with poorer OS. Thus, our study not only indicates the prognostic value of the CRAFITY score for OS in this patient population but also emphasizes the potential superiority of the CRP/Alb ratio as a prognostic biomarker. Further large-scale studies are needed to validate their comparative predictive performance and explore the potential benefits of combining these markers for clinical applications.

Our study included two standard transcatheter intra-arterial therapies. In our cohort, over half (55.64%) of the patients were classified as BCLC stage C, a stage typically associated with higher tumor burden and increased risk of major vascular invasion. It has been reported that HAIC significantly improves OS in patients with unresectable large HCC compared to TACE as first-line treatment.[6] One clinical trial,[40] along with several retrospective studies,[41–43] has demonstrated the efficacy of HAIC in combination with targeted therapies and immunotherapies for the treatment of HCC. However, the optimal transcatheter intra-arterial therapies for unresectable HCC in combination with systemic therapies remains inconclusive. In our subgroup analysis, regardless of the intra-arterial therapies or systemic therapy regimen, HCC patients with a high CRP/Alb ratio consistently exhibited poorer OS. These findings strongly support the CRP/Alb ratio as a broadly applicable and effective prognostic marker for patients undergoing combination therapy. However, for PFS, the CRP/Alb ratio demonstrated significant prognostic value only in patients treated with intra-arterial therapies combined with lenvatinib and immunotherapy. This may be attributed to the sample size, as over half of the patients (54.14%) in this study were treated with lenvatinib-based combination therapy. As one of the first-line recommended agents for HCC, lenvatinib has been reported to show comparable clinical efficacy to atezolizumab combined with bevacizumab.[44,45] These results suggest that the CRP/Alb ratio may provide guidance in selecting patients most likely to benefit from transcatheter intra-arterial therapies combined with lenvatinib and immunotherapy, and offer valuable insights for biomarker exploration in related clinical trials.

In addition to its prognostic value for survival, our study identified the CRP/Alb ratio as a significant predictive marker for TRAEs in patients undergoing combination therapy. Specifically, a higher CRP/Alb ratio was strongly associated with an increased incidence of fever and fatigue. These findings align with studies evaluating the CRAFITY score in HCC patients treated with atezolizumab plus bevacizumab[19] or locoregional-immunotherapy.[39] In these studies, higher scores were similarly linked to a greater frequency of fever, fatigue, and decreased appetite. The mechanisms underlying these associations remain poorly understood. One possible explanation is that elevated CRP levels reflect heightened systemic inflammation, which may drive cancer-related symptoms such as anorexia, weight loss, and fatigue.[14]

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Second, the relatively small sample size underscores the need for larger, multicenter prospective cohort studies to validate these results. Third, the study cohort predominantly consisted of patients with HBV-related HCC (84.96%), limiting the applicability of the findings to non-HBV-related HCC. Further research is needed to explore the prognostic value of the CRP/Alb ratio in diverse etiological populations. Fourth, the inclusion of patients receiving various transcatheter intra-arterial therapies and systemic agents introduces heterogeneity. However, this diversity reflects real-world clinical practice, as combination therapy for HCC continues to evolve. To minimize potential bias, we restricted the analysis to patients who initiated systemic therapy within 30 days before or after intra-arterial treatment and performed stratified analyses. Finally, this study focused on baseline CRP and albumin levels. The prognostic significance of dynamic changes in the CRP/Alb ratio during treatment and follow-up remains an area for further investigation.

Conclusion

In conclusion, the CRP/Alb ratio is an independent and significant predictor of OS and TRAEs in patients with HCC receiving transcatheter intra-arterial therapies combined with MTAs and PD-1/PD-L1 inhibitors. Furthermore, this ratio also demonstrates significant prognostic value for PFS in HCC patients undergoing lenvatinib-based combination therapy. These findings highlight the CRP/Alb ratio as a cost-effective, readily accessible, and reliable biomarker for

predicting outcomes in this patient population. Future studies in larger cohorts are warranted to further validate its clinical utility.

Abbreviations

CRP/Alb, C-reactive protein to albumin; HCC, hepatocellular carcinoma; PD-1/PD-L1, programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors; MTAs, molecular targeted agents; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; OS, overall survival; ROC, receiver operation characteristics; AUC, area under curve; AFP, alpha-fetoprotein; C-reactive protein and alpha-fetoprotein in immunotherapy (CRAFITY) score; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PNI, prognostic nutritional index; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TRAEs, treatment-related adverse events; IQR, interquartile range; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

Data Sharing Statement

Anonymized data available from the corresponding author upon reasonable request.

Ethics and Patients Statements

This retrospective study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Given its retrospective design and the secure handling of patient data, the Independent Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College waived the requirement for informed consent (IRB approval number: 24/175-4455).

All patient data have been anonymized to eliminate any identifying information, securely stored with restricted access, and utilized solely for research purposes.

Author Contributions

All authors made significant contributions to this work, whether in conceptualization, study design, execution, data collection, data analysis, and writing, or all of these; participated in drafting, revising, or critically reviewing the article; agreed on the journal to which the article should be submitted; and agreed to accept responsibility for all aspects of the work. All authors reviewed and approved the final manuscript.

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Disclosure

The authors have no conflicts of interest to report in this study.

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