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ORIGINAL RESEARCH

C-Reactive Protein-Albumin Ratio (CAR): A More Promising Inflammation-Based Prognostic Marker for Patients Undergoing Curative Hepatectomy for Hepatocellular Carcinoma

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Background: Systemic inflammatory response is a hallmark of cancer and plays a significant role in the development and progression of various malignant tumors. This research aimed to estimate the prognostic function of the C-reactive protein-albumin ratio (CAR) in patients undergoing hepatectomy for hepatocellular carcinoma (HCC) and compare it with other inflammation-based prognostic scores, including the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, monocyte-lymphocyte ratio, systemic immune inflammation index, prognostic index, Glasgow prognostic score, and modified Glasgow prognostic score.

Methods: Retrospective analysis was conducted on data from 1039 HCC cases who underwent curative liver resection. The prognostic performance of CAR was compared with other scores using the area under the time-dependent receiver operating characteristic (t-ROC) curve. Multivariable Cox regression analyses were performed to confirm independent predictors for disease-free survival (DFS) and overall survival (OS).

Results: The area under the t-ROC curve for CAR in the evaluation of DFS and OS was significantly greater than that of other scores and alpha-fetoprotein (AFP). Patients were stratified based on the optimal cut-off value of CAR, and the data revealed that both DFS and OS were remarkably worse in the high-CAR set compared to the low-CAR set. Multivariable Cox analysis demonstrated that CAR was an independent prognostic parameters for assessing DFS and OS. Regardless of AFP levels, all patients were subsequently divided into significantly different subgroups of DFS and OS based on CAR risk stratification. Similar results were observed when applying CAR risk stratification to other scoring systems. CAR also showed good clinical applicability in patients with different clinical features.

Conclusion: CAR is a more effective inflammation-based prognostic marker than other scores and AFP in predicting DFS as well as OS among patients with HCC after curative hepatectomy.

Keywords: hepatocellular carcinoma, hepatectomy, systemic inflammation response, inflammation-based prognostic marker, C-reactive protein to albumin ratio

Introduction

Hepatectomy is a major radical therapy method for resectable hepatocellular carcinoma (HCC) patients.[1–3] However, the majority of experience high recurrence rates after surgery, leading to unsatisfactory long-time survival.[4] Thus, the recognition of high-risk patients with poor outcomes using an accurate, efficient, and convenient preoperative model is of great significance allowing for the optimization of adjuvant therapy and improvement of the long-term prognosis for patients.

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Currently, growing research has revealed that systemic inflammatory response (SIR) exerts a key effect in tumorigenesis and progression, and is relevant to the adverse outcomes of many patients with malignant tumors.[5–8] Numerous researches have determined the relevance of inflammation-based prognostic scores (IBPS) to the prognosis of multiple types of tumors.[9,10] These IBPSs typically consist of acute phase proteins and leukocytes from the circulatory system. The neutrophil lymphocyte ratio (NLR), a predictive model on the basis of circulating leukocytes, has been extensively studied[11] and has shown satisfactory prognostic value in different cancer patients.[12–14] Other studies have also found that the platelet lymphocyte ratio (PLR),[15,16] monocyte lymphocyte ratio (MLR),[17,18] systemic immune inflammation index (SII)[19,20] as well as prognostic index (PI)[10,21] are closely involved in the outcomes of many cancer patients. Nevertheless, a significant proportion of HCC patients receive adjuvant therapy before hepatectomy, such as hepatic artery infusion chemotherapy, targeted therapy, and radiofrequency ablation, which can reduce the number of circulating inflammatory cells, such as neutrophils, lymphocytes, monocytes, and platelets.[22] Hence, the leukocyte-based models mentioned above may not accurately assess the true SIR status of HCC patients and may be insufficient in evaluating the prognosis of HCC patients who have undergone hepatectomy.

Additionally, nutritional status is another important indicator closely linked to the adverse outcomes of many cancer patients.[23,24] Poor nutritional status results in increased susceptibility to infection, vascular wall fragility, impaired wound healing, and impaired coagulation function, which increases the risk of serious postoperative complications and may even lead to death.[25–27] Serum C-reactive protein (CRP) and albumin are two important acute-phase proteins that reflect the nutritional condition of the body during SIR.[7] They are involved in the survival prognosis of cancer patients. The Glasgow prognostic score (GPS)[28,29] and modified GPS (mGPS),[30,31] which are composed of these two major acute-phase proteins involved in SIR, have been considered independent prognostic markers for various malignancies. Recently, the CRP to albumin ratio (CAR), also based on serum C-reactive protein and albumin, has been thought to be associated with poor prognosis in patients with sepsis and acute hospitalization.[32,33] Growing data revealed that CAR is a new, reliable, and valid prognostic marker for many cancer patients.[34–36] However, as HCC is a malignant tumor with diverse biological behavior, which may affect the clinical profile of inflammation-related markers, the clinical value of IBPS in evaluating the outcomes of patients with HCC remains unclear.

Thus, this research was conducted to assess the clinical practicability of CAR in evaluating the outcomes of HCC patients who subjected to curative hepatic resection, and to compare it with others IBPSs, including NLR, PLR, MLR, SII, PI, GPS, and mGPS.

Patients and Methods

Patients

In this research, those HCC patients who subjected to initial curative liver resection at the Guangxi Medical University Cancer Hospital from September 2013 to June 2019 were enrolled. Patients who had undergone other anti-cancer therapies prior to hepatic resection were excluded. This project was ethically approved by Guangxi Medical University Cancer Hospitals and followed guidelines set out by the Helsinki Declaration. In addition, since this is a retrospective research, written informed consent was not needed.

Diagnosis and Definitions

Diagnosis of cirrhosis and HCC were confirmed by postoperative pathology. The Barcelona Clinic Liver Cancer (BCLC) staging system was used for HCC staging.[1] Patients who suffered form esophagogastric varices with thrombocytopenia or splenomegaly were regarded as clinically significant portal hypertension (CSPH).[37] Curative hepatic resection was considered to be complete removal of visible tumors with no remaining tumor cells at the resection edge. Patients who had three or more liver segments removed were classified as having a major hepatectomy.[38]

Definition of Inflammation-Based Prognostic Models

The specific formula of these IBPSs were shown in the Supplementary Table 1. All the indexes in the formula were the results collected for the first time after admission.

Surgery and Follow-Up

Hepatectomy was performed on patients included in this study who had good liver function and resectable tumors on preoperative imaging. Surgery-related information has been described in our previous research.[39]

Routine follow-up was performed after operation. These cases were followed up for 1 month after hepatectomy and every 3 months thereafter. The time of death or withdrawal was used as the end date of the follow-up. During each admission check-up, AFP levels, liver function test, and abdominal computed tomography scans or other imaging examinations were routinely conducted. The patients were remedied through reoperation, transcatheter arterial chemoembolization, radiofrequency or targeted therapy for the recurrence of HCC. The definition of disease-free survival (DFS) and overall survival (OS) as described in our previous study.[40,41]

Statistical Analysis

The χ^2 test was applied to compare categorical indicators, which are shown as n (%), while the Mann–Whitney *U*-test was applied to compare continuous parameters, which are showed as Medians (IQR 25–75).

The predictive power of different IBPSs for DFS and OS was compared using the time-dependent receiver operating characteristic (t-ROC) curves.[41] The optimal cut-off point of the 5-year OS was determined through X-tile analysis.[42] The Kaplan-Meier (KM) curves was applied to assess DFS and OS, and the Log rank test was performed for comparisons between groups. Independent prognostic indexes of DFS and OS were confirmed by multivariable Cox regression analysis, and the statistically significant indexes in univariate analyses were incorporated into the multivariate Cox analysis.

SPSS (v26.0), R Studio (v4.2.2) and X-Tile (v3.6.1) software were used for statistics and analyses. A P value of < 0.05 was regarded to indicate statistical significance.

Results

Characteristics of Patients

The detailed clinicopathological features of the 1039 HCC cases are summarized in Table 1. The majority of cases were males, with a median age of 52 and good hepatic function reserve. Among them, 84.5% of the cases were infected with

Table 1 Clinicopathological Characteristics of 1502 Patients with HCC and Different CAR Risk Groups

Variables	Total (n = 1039)	Low CAR (n = 603)	High CAR (n = 436)	*P* value
Age (years)	52 (44, 60)	52 (45, 61)	51 (43, 59)	0.046
Sex				0.258
Male	898 (86.4)	515 (85.4)	383 (87.8)	
Female	141 (13.6)	88 (14.6)	53 (12.2)	
Positive HBsAg	878 (84.5)	501 (83.1)	377 (86.5)	0.137
HBV-DNA, IU/mL				< 0.001
≥ 2000	517 (49.8)	257 (42.6)	260 (59.6)	
< 2000	522 (50.2)	346 (57.4)	176 (40.4)	
Platelet count (10^9/L)	203.0 (157.9, 262.0)	187.0 (148.2, 228.0)	241.0 (183.5, 304.5)	< 0.001
Neutrophil count (10^9/L)	3.7 (2.8, 4.8)	3.3 (2.6, 4.2)	4.4 (3.4, 5.7)	< 0.001
Lymphocyte count (10^9/L)	1.8 (1.4, 2.2)	1.9 (1.5, 2.3)	1.7 (1.4, 2.1)	< 0.001
Monocyte count (10^9/L)	0.5 (0.4, 0.6)	0.4 (0.3, 0.5)	0.6 (0.4, 0.7)	< 0.001
Total bilirubin (μmol/L)	14.3 (10.6, 18.7)	14.1 (10.7, 18.0)	14.7 (10.5, 20.3)	0.037
Prealbumin (mg/L)	177.0 (135.0, 221.0)	196.0 (159.0, 237.5)	141.0 (102.5, 185.0)	< 0.001
Albumin (g/L)	38.2 (35.6, 41.0)	39.4 (36.8, 42.1)	36.4 (33.7, 39.2)	< 0.001

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 1039)	Low CAR (n = 603)	High CAR (n = 436)	*P* value
ALT (U/L)	35.0 (24.0, 53.0)	34.0 (24.0, 49.0)	37.0 (24.0, 57.0)	0.022
AST (U/L)	39.0 (30.0, 58.3)	35.0 (28.0, 47.0)	51.0 (34.0, 72.0)	< 0.001
Creatinine (μmol/L)	77.0 (67.0, 87.0)	78.0 (68.0, 88.0)	75.0 (65.0, 87.0)	0.021
Prothrombin time (s)	12.8 (12.0, 13.6)	12.7 (11.9, 13.3)	12.9 (12.1, 14.0)	0.002
INR	1.07 (1.01, 1.14)	1.06 (1.01, 1.12)	1.09 (1.02, 1.18)	0.002
C-reaction protein (mg/L)	2.7 (1.2, 9.5)	1.3 (0.7, 2.1)	13.2 (7.0, 26.3)	< 0.001
Child-Pugh grade				< 0.001
A	960 (92.4)	25 (4.1)	54 (12.4)	
B	79 (7.6)	578 (95.9)	382 (87.6)	
AFP (ng/mL)				< 0.001
≥ 400	424 (40.8)	214 (35.5)	210 (48.2)	
< 400	615 (59.2)	389 (64.5)	226 (51.8)	
NLR	2.0 (1.5, 2.9)	1.8 (1.4, 2.3)	2.6 (1.8, 3.9)	< 0.001
PLR	111.9 (83.7, 155.0)	99.1 (75.4, 129.8)	139.9 (102.7, 190.3)	< 0.001
MLR	0.3 (0.2, 0.4)	0.2 (0.2, 0.3)	0.3 (0.3, 0.5)	< 0.001
SII	416.7 (258.2, 655.9)	328.6 (215.2, 482.8)	612.2 (375.5, 957.5)	< 0.001
PI	0 (0, 1)	0 (0, 0)	1 (0, 1)	< 0.001
GPS	0 (0, 1)	0 (0, 0)	1 (0, 1)	< 0.001
mGPS	0 (0, 0)	0 (0, 0)	1 (0, 1)	< 0.001
CAR	0.07 (0.03, 0.27)	0.03 (0.02, 0.05)	0.36 (0.18, 0.72)	< 0.001
CSPH	104 (10.0)	61 (10.1)	43 (9.9)	0.893
Ascites	114 (11.0)	40 (6.6)	74 (17.0)	< 0.001
Cirrhosis	510 (49.1)	288 (47.8)	222 (50.9)	0.315
Tumor size (cm)				< 0.001
≥ 5	624 (60.1)	292 (48.4)	332 (76.1)	
< 5	415 (39.9)	311 (51.6)	104 (23.9)	
Tumor number				0.498
Multiple	277 (26.7)	156 (25.9)	121 (27.8)	
Single	763 (73.3)	447 (74.1)	315 (72.2)	
MaVI	248 (23.9)	92 (15.3)	156 (35.8)	< 0.001
BCLC stage				< 0.001
0/A	569 (54.8)	380 (63.0)	189 (43.3)	
B	217 (20.9)	132 (21.9)	85 (19.5)	
C	253 (24.4)	91 (15.1)	162 (37.2)	
Operation time(min)	200 (165, 250)	190 (150, 234)	220 (180, 270)	< 0.001
Blood loss (mL)				< 0.001
≥ 400	356 (34.3)	162 (26.9)	194 (44.5)	
< 400	683 (65.7)	441 (73.1)	242 (55.5)	
Blood transfusion	158 (15.2)	70 (11.6)	88 (20.2)	< 0.001
Extent of resection				< 0.001
Major-hepatectomy	528 (50.8)	260 (43.1)	268 (61.5)	
Minor-hepatectomy	511 (49.2)	343 (56.9)	168 (38.5)	

Note: Continuous data are show as median (25th-75th interquartile range) and categorical data are expressed as n (%).

Abbreviations: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBV-DNA. hepatitis B virus DNA load; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; CAR, c-reaction protein-albumin ratio; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune–inflammation index; PI, prognostic index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; CSPH, clinically significant portal hypertension; MaVI, macrovascular invasion; BCLC, Barcelona Clinical Liver Cancer.

hepatitis B virus (HBV), 49.1% had liver cirrhosis, and 10.0% had CSPH. Based on the BCLC grade, grade 0 and A accounted for 54.8%, grade B accounted for 20.9%, and grade C accounted for 24.4%. In addition, 528 patients underwent major hepatectomy, while 511 patients underwent minor hepatectomy.

Performance of the Prognostic Models in Predicting DFS or OS

Based on the t-ROC curve analysis, we concluded that the CAR has a stronger predictive ability to evaluate OS compared to other IBPSs, including NLR, PLR, MLR, SII, PI, GPS, and mGPS (Figure 1A). Similarly, when assessing DFS at each time point after hepatectomy, CAR showed a larger area under the curve (AUC) compared to other IBPSs (Figure 1B). Furthermore, CAR also showed higher predictive performance for both OS and DFS compared to alpha-fetoprotein (AFP). The AUC values of CAR to predict the 1-, 3-, and 5-year DFS were 0.65, 0.69, and 0.67, respectively. Additionally, the AUC values for OS were 0.69, 0.68, and 0.69, respectively (Supplementary Table 2).

Stratification of Prognostic Models

As presented in Supplementary Figure 1, the optimal cut-off values for NLR, PLR, MLR, SII, and CAR were confirmed as 3.4, 146.5, 0.3, 994.5, and 0.11, respectively. Subsequently, all cases were classified into high CAR (> 0.11, n = 436) and low CAR (≤ 0.11, n = 603) sets based on the optimal CAR cut-off value for further analysis.

Relationship Between CAR and Clinicopathological Parameters

As presented in Table 1, higher CAR values were associated with increased levels of inflammation markers (platelet, lymphocyte, and neutrophil counts), impaired hepatic function (lower levels of prealbumin and albumin; higher levels of total bilirubin, ALT, and AST), poorer surgical condition (larger extent of resection, greater blood loss and transfusion, and longer operation times), more advanced tumor status (with macroscopic vascular invasion [MaVI], larger tumor size, and advanced BCLC stage), and a higher prevalence of CSPH and cirrhosis. Additionally, patients with high CAR also had higher levels of NLR, PLR, MLR, SII, PI, GPS, and mGPS ($P < 0.05$ for all).

Correlation Between CAR and DSF or OS

During a median follow-up of 46 months (17–62), a total of 538 cases (51.7%) experienced tumor recurrence, including 268 patients (61.5%) in the high-CAR set as well as 270 patients (44.8%) in the low-CAR set ($P < 0.05$). Patients with a high CAR value had remarkably lower 1-, 3-, and 5-year DFS rates (39.6%, 23.5%, and 15.0%, respectively) in contrast with those with a low CAR value (67.0%, 47.6%, and 36.2%, respectively; see Figure 2A and Supplementary Table 3; $P < 0.05$ for all).

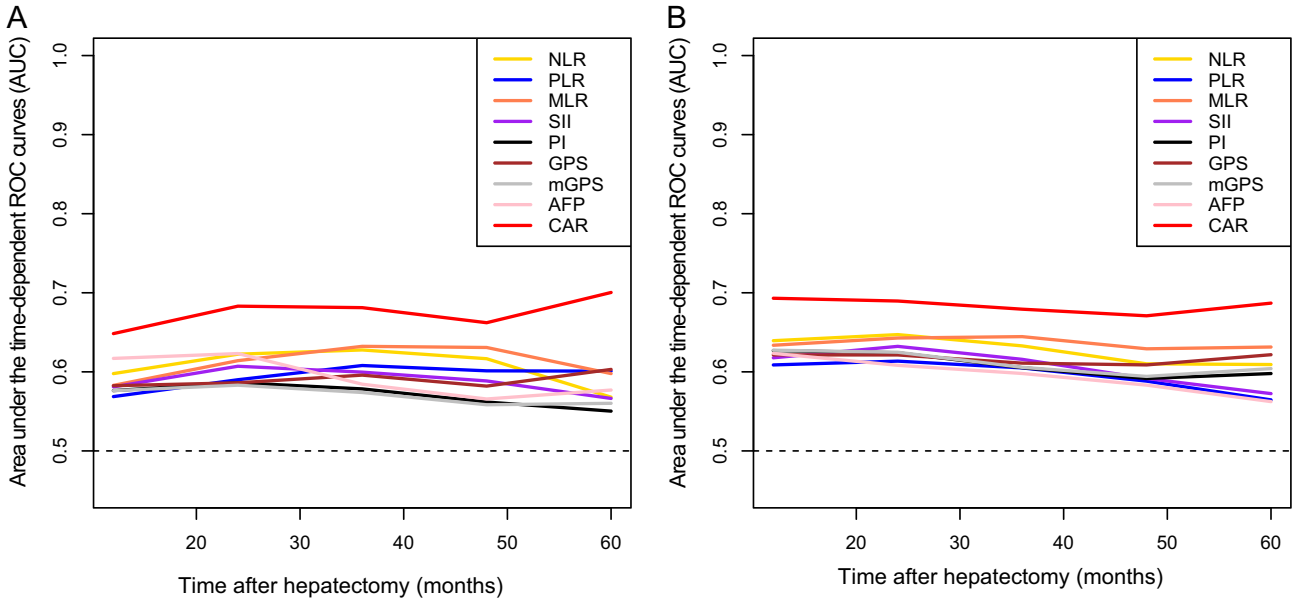

Figure 1 The t-ROC curves analyses to compare the predictive efficiencies of NLR, PLR, MLR, SII, PI, GPS, mGPS, AFP and CAR in assessing (**A**) DFS and (**B**) OS.
Abbreviations: t-ROC, time-dependent receiver operating characteristic curve; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune–inflammation index; PI, prognostic index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; AFP, alpha-fetoprotein; CAR, C-reaction protein-albumin ratio; DFS disease-free survival; OS overall survival.

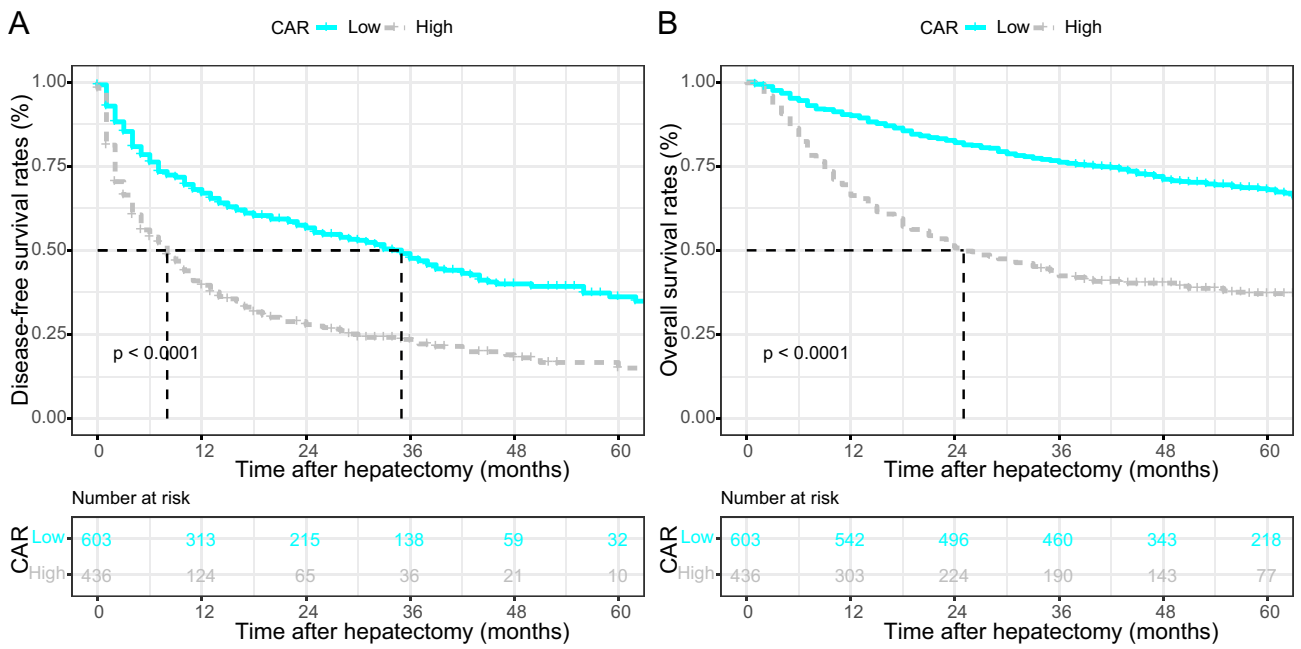

Figure 2 Relationship between the two CAR groups and (**A**) DFS or (**B**) OS in patients with HCC who underwent hepatectomy ($P < 0.001$ for both).
Abbreviations: DFS, disease-free survival; OS, overall survival; CAR, C-reaction protein-albumin ratio.

Furthermore, 468 patients (45.0%) died during the median follow up, with 273 deaths (62.6%) occurring in the high-CAR set as well as 195 deaths (32.3%) in the low-CAR set ($P < 0.05$). The 1-, 3-, and 5-year OS rates of patients with a high CAR value (66.3%, 42.4%, and 37.1%, respectively) were greatly lower in contrast with those with a low CAR value (90.0%, 76.2%, and 68.0%, respectively; Figure 2B and Supplementary Table 3; $P < 0.05$ for all).

Univariable and Multivariable Analyses for DFS

As presented in Table 2, the univariable Cox regression analysis showed significant associations between these IBPSs and DFS, as well as male sex, age, tumor size, MaVI, AFP, HBV-DNA, HBsAg, Child-Pugh, CSPH, ascites, operation time, major hepatectomy, blood loss, and transfusion. The multivariable analysis indicated that CAR was an independent risk parameter of DFS, along with male sex, NLR, AFP, ascites, blood loss, as well as major hepatectomy.

Table 2 Univariable and Multivariable Analyses to Identify Independent Prognostic Indicators of Disease-Free Survival in Patients with HCC

Variables	Disease-Free Survival			
	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	0.991 (0.983, 0.998)	0.014	1.000 (0.992, 1.009)	0.911
Male Sex	1.332 (1.012, 1.753)	0.041	1.364 (1.031, 1.805)	0.030
Positive HBsAg	1.414 (1.089, 1.836)	0.009	1.133 (0.843, 1.523)	0.409
HBV-DNA ≥ 2000 IU/mL	1.499 (1.263, 1.778)	< 0.001	1.174 (0.966, 1.426)	0.107
Child-Pugh grade B	1.430 (1.035, 1.975)	0.030	0.710 (0.466, 1.084)	0.113
AFP ≥ 400 ng/mL	1.784 (1.505, 2.115)	< 0.001	1.493 (1.247, 1.788)	< 0.001
NLR	1.712 (1.386, 2.113)	< 0.001	1.415 (1.038, 1.929)	0.028
PLR	1.442 (1.201, 1.732)	< 0.001	0.997 (0.796, 1.249)	0.981
MLR	1.532 (1.289, 1.820)	< 0.001	1.002 (0.813, 1.235)	0.983
SII	1.857 (1.451, 2.377)	< 0.001	1.023 (0.707, 1.480)	0.905
PI	1.680 (1.398, 2.020)	< 0.001	0.985 (0.482, 2.015)	0.967

(*Continued*)

Table 2 (Continued).

Variables	Disease-Free Survival			
	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
GPS	1.610 (1.354, 1.914)	< 0.001	1.149 (0.848, 1.556)	0.371
mGPS	1.713 (1.421, 2.065)	< 0.001	0.692 (0.317, 1.512)	0.356
CAR	2.088 (1.760, 2.478)	< 0.001	1.652 (1.295, 2.107)	< 0.001
CSPH	1.377 (1.055, 1.798)	0.019	1.173 (0.887, 1.551)	0.264
Ascites	1.657 (1.286, 2.136)	< 0.001	1.404 (1.010, 1.951)	0.043
Cirrhosis	1.165 (0.983, 1.380)	0.077		
Tumor size ≥ 5 cm	1.647 (1.376, 1.972)	< 0.001	1.048 (0.856, 1.283)	0.652
Multiple tumor number	1.069 (0.883, 1.294)	0.495		
MaVI	2.286 (1.900, 2.752)	< 0.001	1.216 (0.466, 3.173)	0.690
BCLC stage				
0/A	Ref	Ref	Ref	Ref
B	1.368 (1.097, 1.704)	0.005	0.809 (0.305, 2.147)	0.671
C	2.566 (2.106, 3.127)	< 0.001	0.670 (0.254, 1.764)	0.417
Operation time(min)	1.002 (1.001, 1.003)	< 0.001	1.000 (0.999, 1.001)	0.887
Blood loss ≥400 mL	1.922 (1.618, 2.282)	< 0.001	1.346 (1.100, 1.647)	0.004
Blood transfusion	1.487 (1.189, 1.859)	0.001	1.089 (0.852, 1.391)	0.496
Major-hepatectomy	1.679 (1.414, 1.994)	< 0.001	1.331 (1.094, 1.620)	0.004

Abbreviations: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBV-DNA. hepatitis B virus DNA load; AFP, alpha-fetoprotein; CAR, c-reaction protein-to-albumin ratio; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune–inflammation index; PI, prognostic index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; CSPH, clinically significant portal hypertension; MaVI, macrovascular invasion; BCLC, Barcelona Clinical Liver Cancer.

Univariable and Multivariable Analyses for OS

As presented in Table 3, the univariable Cox regression analysis demonstrated significant associations between theses IBPSs and OS, as well as AFP, HBsAg, HBV-DNA, age, tumor size, blood loss, and transfusion, BCLC stage, Child-Pugh grade B, ascites, MaVI, major hepatectomy, and operation time. In the multivariable analysis, CAR was considered

Table 3 Univariable and Multivariable Analyses to Identify Independent Prognostic Indicators of Overall Survival in Patients with HCC

Variables	Overall Survival			
	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	0.991 (0.983, 0.998)	0.019	1.001 (0.992, 1.010)	0.818
Male Sex	1.202 (0.911, 1.586)	0.193		
Positive HBsAg	1.325 (1.008, 1.741)	0.044	1.055 (0.769, 1.448)	0.740
HBV-DNA ≥ 2000 IU/mL	1.628 (1.354, 1.958)	< 0.001	1.325 (1.071, 1.639)	0.010
Child-Pugh grade B	1.543 (1.141, 2.086)	0.005	0.745 (0.490, 1.132)	0.167
AFP ≥ 400 ng/mL	1.732 (1.445, 2.077)	< 0.001	1.311 (1.082, 1.587)	0.006
NLR	2.315 (1.883, 2.847)	< 0.001	1.814 (1.337, 2.463)	< 0.001
PLR	1.672 (1.384, 2.020)	< 0.001	0.938 (0.744, 1.183)	0.590
MLR	1.969 (1.642, 2.362)	< 0.001	1.081 (0.867, 1.349)	0.490
SII	2.295 (1.800, 2.925)	< 0.001	0.950 (0.659, 1.369)	0.782
PI	2.219 (1.762, 2.572)	< 0.001	0.724 (0.296, 1.776)	0.481

(*Continued*)

Table 3 (Continued).

Variables	Overall Survival			
	Univariable		Multivariable	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
GPS	1.967 (1.639, 2.359)	< 0.001	1.267 (0.921, 1.744)	0.146
mGPS	2.225 (1.839, 2.692)	< 0.001	1.003 (0.385, 2.612)	0.996
CAR	2.681 (2.229, 3.226)	< 0.001	1.649 (1.277, 2.130)	< 0.001
CSPH	1.263 (0.951, 1.677)	0.107		
Ascites	1.668 (1.295, 2.147)	< 0.001	1.270 (0.903, 1.788)	0.170
Cirrhosis	1.157 (0.965, 1.387)	0.116		
Tumor size ≥ 5 cm	2.220 (1.809, 2.725)	< 0.001	1.307 (1.046, 1.633)	0.018
Multiple tumor number	0.922 (0.746, 1.140)	0.455		
MaVI	3.044 (2.524, 3.671)	< 0.001	2.155 (0.849, 5.473)	0.106
BCLC stage				
0/A	Ref		Ref	
B	3.507 (2.856, 4.305)	< 0.001	1.190 (0.461, 3.071)	0.720
C	1.544 (1.209, 1.972)	0.001	0.896 (0.351, 2.286)	0.818
Operation time(min)	1.003 (1.002, 1.004)	< 0.001	1.001 (0.999, 1.002)	0.324
Blood loss ≥400 mL	1.980 (1.650, 2.376)	< 0.001	1.200 (0.972, 1.481)	0.090
Blood transfusion	1.418 (1.117, 1.802)	0.004	1.134 (0.879, 1.463)	0.332
Major-hepatectomy	1.777 (1.475, 2.140)	< 0.001	1.299 (1.054, 1.602)	0.014

Abbreviations: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBV-DNA. hepatitis B virus DNA load; AFP, alpha-fetoprotein; CAR, c-reaction protein-to-albumin ratio; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SII, systemic immune–inflammation index; PI, prognostic index; GPS, Glasgow Prognostic Score; mGPS, modified Glasgow Prognostic Score; CSPH, clinically significant portal hypertension; MaVI, macrovascular invasion; BCLC, Barcelona Clinical Liver Cancer.

an independent predictor of OS, along with other factors including NLR, HBV-DNA, tumor size, AFP, and major hepatectomy.

Subgroup Analyses

To further validate the predictive value of CAR, a stratified risk analysis was performed based on different levels of AFP values. The results showed that these patients with low AFP values (< 400 ng/mL) were classified into two distinct subgroups according to the cut-off value of the CAR, exhibiting markedly different DFS and OS. Similarly, within the high AFP group (≥ 400 ng/mL), patients with a high CAR also had a remarkably worse DFS and OS compared to those with low CAR (Figure 3; $P < 0.001$ for all). Furthermore, CAR demonstrated consistent results across different levels of IBPSs (Supplementary Figures 2–8).

Discussion

In our research, we compared the clinical applicability of different IBPSs in assessing postoperative outcomes among patients with HCC who underwent curative liver resection. We discovered that the preoperative CAR demonstrated a significantly superior predictive ability for DFS as well as OS compared to other scores and AFP. Furthermore, through Cox multivariate analysis, CAR was determined to be an independent prognostic marker for DFS and OS. Additionally, when compared to AFP, CAR showed more consistent prognostic value and higher predictive efficiency for patients with diverse characteristics. Therefore, the preoperative CAR is considered a more valuable IBPS for HCC patients undergoing curative hepatectomy.

Currently, the important effect of SIR in the occurrence and development of malignant tumors has been confirmed by several studies.[5–8] This process appears to involve bidirectional interactions, where inflammation can be both a response to growing tumor cells and a contributor to their occurrence and progression. Notably, tumor-related inflammation is also

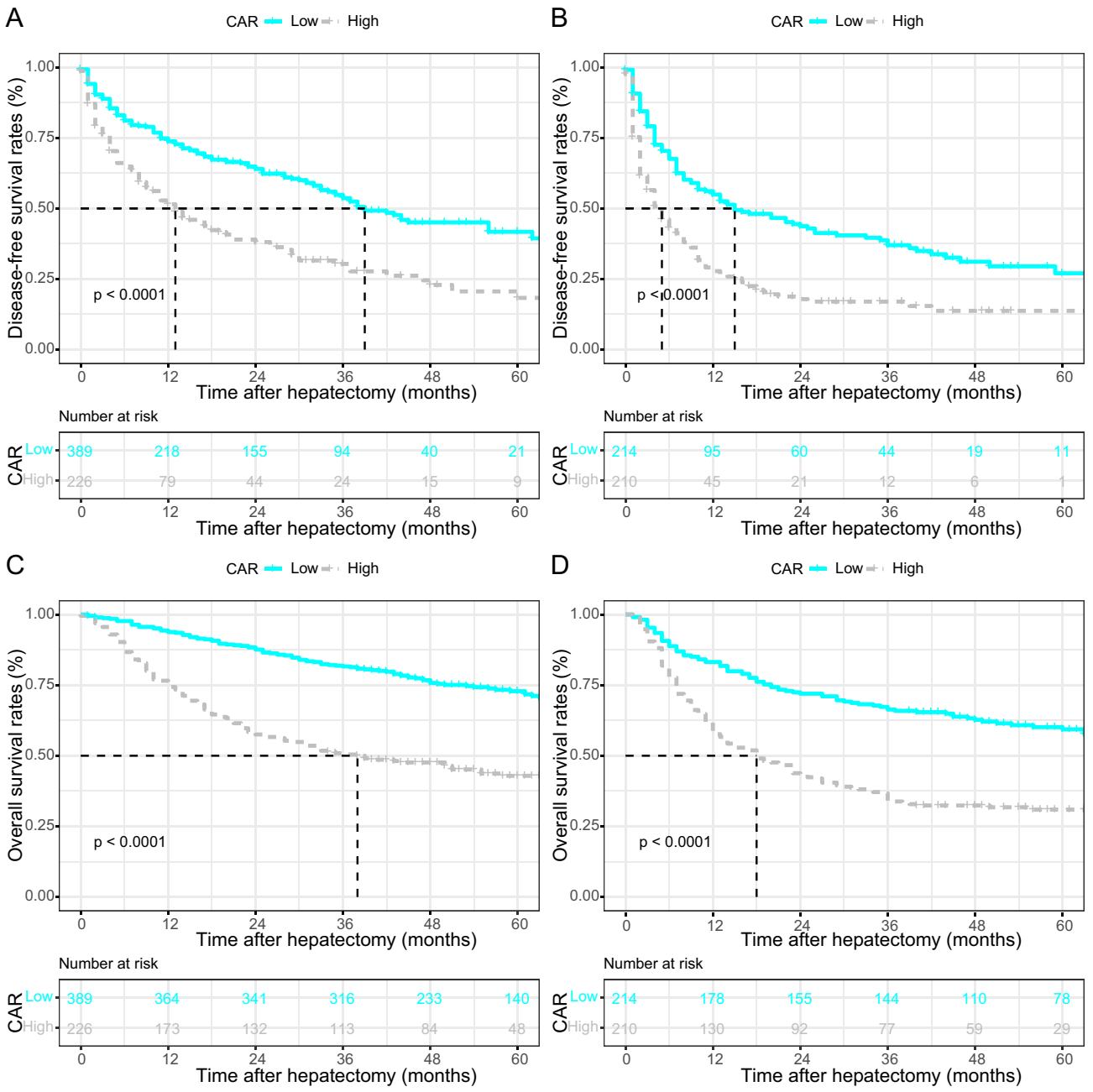

Figure 3 Subgroups analyses of DFS and OS was performed in patients with high and low CAR based on AFP values. (**A**) DFS in patients with low AFP ($P < 0.001$); (**B**) DFS in patients with high AFP ($P < 0.001$); (**C**) OS in patients with low AFP ($P < 0.001$); and (**D**) OS in patients with high AFP ($P < 0.001$).
Abbreviations: DFS, disease-free survival; OS, overall survival; CAR, C-reaction protein-albumin ratio; AFP, alpha-fetoprotein.

implicated in tumor recurrence after curative liver resection for HCC. It may be attributed to high-risk factors and the original disease status, reflecting the bidirectional nature of inflammation in oncogenesis. Inflammatory cytokines and chemokines produced by SIR, particularly interleukin-6 (IL-6), promote the occurrence as well as the development of malignancies by triggering relevant signaling pathways in the tumor microenvironment.[43–45] Specifically, IL-6, as an inflammation-associated cancer cytokine, leads to malignant biological changes such as metastasis, drug resistance, and hepatocyte proliferation through activating the IL-6/STAT3 pathway, which is one of the main ways that participates in the occurrence of HCC.[46,47] Additionally, IL-6 not only inhibits albumin synthesis but also regulates its production along with CRP synthesis in the liver.[48] Therefore, the presence of SIR is often accompanied by an increase in serum CRP value and a decrease in serum albumin value. Many researches have revealed that high preoperative serum CRP levels

are strongly related to a poorer SIR status and worse survival after hepatectomy, making it a potential biomarker for systemic response to cancer growth.[49] Serum albumin levels, on the other hand, are commonly applied to estimate the immune and nutritional condition of individuals. They can inhibit tumor development by stabilizing DNA replication and promoting the body's immune response.[50,51] Albumin can get lower in well nutritional state in the presence of inflammation. Consequently, it is important to note that low albumin levels do not always correlate with poor nutrition. Clinically, low serum levels of albumin often indicate a poor outcome for cancer patients.[25] The combination of serum CRP and albumin (known as CAR) is a novel, reliable, and valid immune-based prognostic score that comprehensively considers the patients' inflammatory status and nutritional situation and was validated in multiple tumors. However, further verification is still required for HCC patients.

In our research, the t-ROC analyses indicated that the CAR significantly outperformed other IBPSs, including PLR, MLR, NLR, SII, PI, GPS, and mGPS, in predicting DFS as well as OS among HCC patients after operation. Subsequently, we confirmed that the optimal cut-off value of CAR was 0.11 through X-tile analysis. Then, all patients were classified into two different risk sets. Further in-depth mining revealed that the high-CAR set had worse tumor status (larger tumor size, presence of MaVI, along with advanced BCLC stage) compared to the low CAR group, indicating that CAR may indicate the progression and metastasis of HCC patients. A series of subsequent survival analyses showed that DFS and OS worsened among the high CAR group. Additionally, multivariate Cox analyses showed that a high CAR value was an independent prognostic factors for DFS and OS in HCC patients after hepatic resection. Thus, we can preliminarily conclude that preoperative CAR provides good prognostic predictability for HCC patients who have undergone liver hepatectomy.

Compared with CAR, other IBPSs evaluated in this research, including NLR, PLR, MLR, SII, PI, GPS, and mGPS, did not show significant predictive ability. NLR, as a predictor of the malignant behavior of HCC, may independently assess the outcomes in HCC patients after hepatectomy.[52] Consistent with previous research reports, NLR was also an independent risk index of DFS and OS in our study, but its prognostic value was significantly worse than that of CAR. Previous research has shown that high preoperative PLR values are linked to poor postoperative outcomes in HCC patients,[53] but it was not significant in our multivariate analysis. Consistent results were observed for MLR, SII, PI, GPS, and mGPS in our research. Notably, although CAR uses the same factors as GPS and mGPS, it can stratify patients' results more carefully and strictly because its continuous properties may be better than scoring serum CRP and albumin levels alone. The poor predictive power of these scores in the multivariate Cox analysis may be due to the fact that the CAR score can stratify patients' results more carefully and strictly because its continuous properties may be better than scoring serum CRP and albumin levels alone. In this research, a high CAR is strongly connected with high NLR, high PLR, high MLR, high SII, high PI, high GPS, and high mGPS. Nevertheless, t-ROC analyses showed that the discriminant ability of these scores for DFS and OS was significantly lower than that of CAR. Therefore, we have come to the further conclusion that CAR may have greater clinical applicability than other scores in estimating the prognosis of HCC patients who have undergone hepatic resection.

At present, AFP is the most widely applied marker for evaluating the prognosis of HCC patients.[54] Our results also revealed that AFP may be an independent marker of DFS as well as OS among HCC patients after operation. Notably, t-ROC analyses revealed that CAR significantly outperformed AFP in predicting DFS and OS. Furthermore, we conducted a series of subgroup analyses based on the optimal cut-off values of CAR, and we found that CAR was superior to AFP in assessing the prognosis of HCC patients who had undergone hepatic resection. Encouragingly, similar findings were acquired when comparing to other prognostic models. Considering the poor prognosis of patients with high CAR, perioperative adjuvant therapy might help decrease the possibility of relapse, improve the quality of life, and increase survival time. Moreover, these cases need to be followed up more closely so that recurrences can be detected and treated earlier.

However, there were also several limitations. Firstly, the majority of the included HCC cases were infected with the HBV. Therefore, further research is needed to investigate whether CAR has a similar predictive value in HCC cases caused by other etiologies. Secondly, additional multi-center projects are necessary to validate our findings. Finally, the optimal cut-off value of CAR may vary among different populations. Thus, further research is required to confirm our conclusions.

Conclusion

Compared with other IBPSs and AFP, preoperative CAR showed a higher predictive value in evaluating DFS and OS in HCC patients after curative hepatectomy. The simplicity, accessibility, and strong clinical applicability of CAR made it as a potentially accurate index for the prognostic assessment of HCC patients undergoing curative hepatectomy.

Abbreviations

AFP, α-fetoprotein; AUC, area under the t-ROC curve; BCLC, Barcelona Clinical Liver Cancer; CAR, CRP to albumin ratio; CRP, C-reactive protein; CSPH, clinically significant portal hypertension; DFS, disease-free survival; GPS, Glasgow prognostic score; HCC, hepatocellular carcinoma; IBPS, inflammation-based prognostic score; NLR, neutrophil-lymphocyte ratio; MaVI, macrovascular invasion; MLR, monocyte-lymphocyte ratio; mGPS, modified Glasgow outcome scale; OS, overall survival; PLR, platelet-lymphocyte ratio; PI, prognostic index; SII, systemic immune-inflammation index; SIR, systemic inflammatory response; t-ROC, time-dependent receiver operating characteristic.

Data Sharing Statement

The data used or analyzed during this study are included in this article and available from the corresponding author (J.-Z.Y.) upon reasonable request.

Ethics Approval and Consent to Participate

This study was supervised by the ethics committee of Guangxi Medical University Cancer Hospital, and written informed consent was not needed since this was a retrospective study by decision of the ethics committee of Guangxi Medical University Cancer Hospital. We confirm that all patient data was treated confidentially. All methods were carried out in accordance with relevant guidelines and regulations. The abstract of this paper was presented at the 2023 Chinese Congress on Holistic Integrative Oncology (CCHIO) as an abstract presentation with interim findings.

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Disclosure

The authors have no conflicts of interest directly relevant to this work.

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