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Prognostic significance of the CRP/Alb and neutrophil to lymphocyte ratios in hepatocellular carcinoma patients undergoing TACE and RFA

Yanjun Shen[1] | Huige Wang[2] | Wendong Li[1] | Jinglong Chen[1] (iD)

[1]Department of Oncology, Beijing Ditan Hospital, Capital Medical University, Beijing, China

[2]Department of Gynecology, Wangjing Hospital of Chinese Academy of Chinese Medical, Beijing, China

Correspondence
Jinglong Chen, Department of Oncology, Beijing Ditan Hospital, Capital Medical University, 8 Jingshun East Street, Chaoyang District, Beijing 100015, China.
Email: dtzlk@sina.com

Abstract

Background: The C-reactive protein (CRP)/albumin (Alb) ratio (CAR) is a basic inflammatory factor that has been related to poor survival of patients with various tumors. Our research retrospectively examined the relationship between the CAR and the prognosis of hepatocellular carcinoma (HCC).

Methods: This study included 172 patients with HCC who were treated with transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA).

Results: The CAR was weakly related to the neutrophil/lymphocyte ratio (NLR, $r = .159$, $P = .037$) and the lymphocyte/monocyte ratio (LMR, $r = -.263$, $P = .001$). The Glasgow Prognostic Score (GPS) (0/1-2) was related to liver cirrhosis ($P = .003$), tumor number ($P = .02$), Child-Pugh grade ($P = .001$), the platelet/lymphocyte ratio (PLR, $P = .006$), and the LMR ($P = .021$). Correlation analysis demonstrated that an elevated CAR was markedly correlated with the tumor size ($P = .019$), alpha-fetoprotein (AFP) level ($P = .033$), thrombosis of the portal vein ($P = .004$), the NLR ($P = .036$), and the LMR ($P = .001$). Multivariate analysis indicated that the prognosis of the CAR-High and NLR-High cohort (mOS = 7 months) was significantly worse than those of the CAR-High or NLR-High cohort (mOS = 15 months) and the CAR-Low and NLR-Low cohort (mOS = 26.5 months).

Conclusions: Combination of the NLR and the CAR represents a convenient, quick, and noninvasive biological marker that could improve prognostic prediction in patients with HCC.

KEYWORDS
C-reactive protein/albumin ratio, hepatocellular carcinoma, inflammation, neutrophil/lymphocyte ratio, overall survival

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Yanjun Shen and Huige Wang contributed equally to this work and should be considered co-first authors.

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) has high morbidity and death rates not only in China, where it, according to the latest report, was the fourth most common type of malignancy and the third most common reason for tumor-associated deaths in 2015, but also in countries in Western and Central Asia.[1,2] Approximately 70%-80% of patients with HCC are diagnosed at terminal stages of the disease.[3] Therefore, many nonsurgical therapies are used, such as transarterial chemoembolization (TACE) and percutaneous radiofrequency ablation (RFA).[4,5] However, despite these advancements, the morbidity and death rates of HCC are increasing.[6] To achieve precise individualized therapy in patients with HCC, the discovery of appropriate markers for proper prognostic evaluation is urgently needed. Serum markers, with their general availability and affordability, are useful for predicting HCC recurrence and survival.[7]

Recently, accumulating evidence has indicated that the systemic inflammatory response (SIR) is pivotal in tumor development.[8] Some proposed inflammatory indicators, including the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), and the C-reactive protein (CRP) level, have been demonstrated to be useful indicators for evaluating the prognosis of the disease and survival of various cancers.[9,10] Currently, the CRP/albumin (Alb) ratio (CAR) has been identified as a new prognostic marker. An increased CAR is related to an unfavorable prognosis of various cancers, for example, cervical cancer and esophageal cancer.[11,12]

Nevertheless, whether the CAR is linked to the prognosis in patients with HCC following TACE and RFA is unknown. Therefore, our study examined the prognostic importance of combining the CAR and the NLR in patients with HCC following TACE and RFA.

2 | MATERIALS AND METHODS

2.1 | Patient selection

Between January 2009 and March 2017, 239 patients with HCC underwent TACE and RFA at Beijing Ditan Hospital, Capital Medical University. Among this group of 239 patients with HCC, serum CRP levels were measured in 172 patients before undergoing TACE and RFA, and these patients were subsequently selected for inclusion in the present study. The clinicopathological characterization was based on the criteria of the American Association for the Study of Liver Disease.[13] The local ethics board approved the research protocols of the present study, which followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from the individual patients. The inclusion criteria were as follows: (a) an Eastern Cooperative Oncology Group Performance Status (ECOG-PS)[14] of 0-1; (b) Child-Pugh Class A or B preoperative liver function; (c) the absence of other tumors affecting prognosis; and (d) no previous treatment for HCC. The exclusion criteria included the following: (a) severe disease, including

heart failure or hepatic failure; (b) esophageal or gastric variceal bleeding within one month; (c) terminal stages of liver disease (bilirubin level >3 mg/dL); and (d) previous anti-inflammatory medications taken within 1 week.

2.2 | TACE procedure

For TACE, the hepatic artery was catheterized via the right common femoral artery under fluoroscopic guidance. The tumor-feeding artery was then identified by common hepatic and superior mesenteric arteriography. A mixture of pirarubicin (15 mg/m^2), hydroxycamptothecin (8 mg/m^2), and lipiodol (5-10 mL) was administered under the control of a fluoroscope until arterial flow stasis was evident.

2.3 | RFA procedure

Radiofrequency ablation was performed on an inpatient basis using an internal cooling rheophore with a 2- or 3-cm exposed tip (Olympus Winter & Ibe GmbH). After the administration of general or local anesthetics, electrode needles were inserted into the tumor percutaneously under contrast-enhanced computed tomography (CT) guidance. The procedures were performed according to the standard technique. Tumor ablation was then performed until the cancer was completely removed, avoiding the intrahepatic bile duct and large vessels. The needle tract was also ablated to stop bleeding and prevent tract seeding. All patients received RFA treatment within 1 week after TACE.

2.4 | Data collection

Data were collected at the time of diagnosis and included patient demographics, tumor size (cm), tumor number, Child-Pugh class, the presence of liver cirrhosis, portal vein tumor emboli, Barcelona Clinic Liver Cancer (BCLC) stage, the serum Alb level (g/dL), the CRP level (mg/dL), the serum alpha-fetoprotein (AFP) level (ng/dL), the complete blood count, and other clinicopathologic parameters.

As described previously,[15] the Glasgow Prognostic Score (GPS) consists of two biochemical indices, namely the CRP level (≤10 mg/L: 0, >10 mg/L: 1) and the Alb level (≥35 g/L: 0, <35 g/L: 1). The sums of the scores of the three groups were 0, 1, or 2. The CAR was defined as the CRP/Alb ratio. The lymphocyte/monocyte ratio (LMR) was defined as the lymphocyte/monocyte ratio. The NLR and the PLR were defined as the neutrophil/lymphocyte and platelet/lymphocyte ratios, respectively. The main end point of this research was overall survival (OS), which was defined as the time from the date of HCC diagnosis to the date of death or last follow-up. The progression-free survival, tumor-specific survival, and treatment response in patients with HCC following TACE and RFA should further be confirmed in future trials.

2.5 | Statistical analysis

Statistical analyses were performed using IBM SPSS 22.0 statistical software (SPSS Inc). Variables with significant prognostic

value according to the Kaplan-Meier analysis were included in the multivariate analysis via Cox regression analysis, which was conducted with the backward step method. Survivorship curves were calculated using the Kaplan-Meier method and examined by log-rank tests. Comparisons of the differences between groups were tested for significance with chi-squared tests for classified variables. The optimal cutoff values for inflammation-based prognostic scores were determined via receiver operating characteristic (ROC) curve analysis. The associations between the CAR and other inflammation-based prognostic markers, for instance, the NLR and the LMR, were analyzed by Spearman's rank correlations. The survival curves and ROC curves were generated via GraphPad Prism 6.0 (GraphPad Software Inc). Two-sided P-values < .05 were deemed statistically significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 172 patients with HCC participated in this study, including 31 women and 141 men (age range: 35-87 years; median age 57 years). The functional liver reserve was Child-Pugh grade A in 109 (63.4%) patients and grade B in 63 (36.6%) patients before TACE and RFA. In our cohort, 46 (26.7%) patients were classified into the positive portal vein thrombosis category, and 126 (73.3%) patients were classified into the negative portal vein thrombosis category. The baseline characteristics of all 172 patients are listed in Table 1.

3.2 | Optimal cutoff values

Receiver operating characteristic curve analysis identified the recommended cutoff values for the preoperative CAR, NLR, PLR, and LMR as 0.275 (range 0.010-1.505, area under the curve (AUC) = 0.813, P = .000), 2.205 (range 0.58-26.82, AUC = 0.629, P = .02), 98.87 (range 14.26-787.14, AUC = 0.662, P = .004), and 2.83 (range 0.58-15.06, AUC = 0.814, P = .001), respectively (Figure 1). Based on the optimal cutoff values, all patients were divided into the following groups: CAR ≤ 0.28 (n = 105), CAR > 0.28 (n = 67), NLR ≤ 2.2 (n = 84), NLR > 2.2 (n = 88), PLR ≤ 98.9 (n = 100), PLR > 98.9 (n = 72), LMR ≤ 2.8 (n = 80), and LMR > 2.8 (n = 92).

3.3 | Survival and prognostic factors

According to the univariate analysis, the tumor size (HR = 1.378 CI: 1.118-1.898, P = .008), Child-Pugh grade (HR = 1.103, CI: 0.849-1.433, P = .001), AFP level (HR = 1.478, CI: 1.081-2.01, P = .03), presence of portal vein thrombosis (HR = 1.819, CI: 1.532-3.101, P = .001), NLR (HR = 1.611, CI: 1.289-2.141, P = .002), LMR (HR = 1.314, CI: 1.043-1.742, P = .027), CAR (HR = 1.493, CI: 1.147-2.259, P = .008), and GPS (HR = 1.511, CI: 1.167-2.123, P = .004) were markedly correlated with OS in all patients (Table 1; Figure 2).

After multivariate Cox regression analysis, the tumor size (HR = 1.561, CI: 1.256-1.941, P = .006), presence of portal vein

thrombosis (HR = 1.712, CI: 1.420-2.062, P = .001), GPS (HR = 1.757, CI: 1.604-1.925, P = .01), CAR (HR = 3.167, CI: 2.588-3.876, P = .001), and NLR (HR = 1.912, CI: 1.713-2.134, P = .003) were all found to be independent prognostic factors of OS in patients with HCC (Table 1; Figure 2).

3.4 | Relationships of the GPS and CAR to other clinicopathological factors

Significant correlations were found between the two GPS (0/1-2) groups and liver cirrhosis (P = .003), the tumor number (P = .02), the Child-Pugh grade (P = .001), the PLR (P = .006), and the LMR (P = .021; Table 2). In addition, the correlation analysis revealed that an elevated CAR was significantly related to tumor size (P = .019), AFP level (P = .033), the presence of portal vein thrombosis (P = .004), the NLR (P = .036), and the LMR (P = .001; Table 2).

Spearman's rank correlation analysis indicated that the CAR was weakly related to the NLR (r = .159, P = .037) and the LMR (r = −.263, P = .001; Figure 3). The combination of the CAR and NLR might improve the clinical prediction of OS in patients with HCC. Therefore, the 172 patients in the present study were assigned to one of the three following cohorts: (a) CAR-High and NLR-High (n = 41), (b) NLR-High or CAR-High (n = 73), or (c) NLR-Low and CAR-Low (n = 58). The ROC curve analysis revealed that the AUC of the combination of the CAR and NLR was 0.824 (P = .001; Figure 4). Finally, the CAR-High and NLR-High cohort (mOS = 7 months) had a significantly worse prognosis than either the CAR-High or NLR-High cohort (mOS = 15 months) or the CAR-Low and NLR-Low cohort (mOS = 26.5 months, Figure 5; Table 1).

4 | DISCUSSION

Accumulating evidence indicates that outcomes for patients with cancer are significantly associated with the level of tumor-associated inflammation.[16] When the growth or invasion of tumors occurs, inflammatory cytokines, for instance, tumor necrosis factor (TNF); interleukin (IL)-6, and −8; and vascular endothelial all growth factor (VEGF), are secreted by cancer cells or tumor-associated lymphocytes, which facilitates angiogenesis and the inhibition of the host immunoreaction, including that involving neutrophils, lymphocytes, platelets, and CRP.[17,18] Therefore, elevated levels or ratios of inflammatory cells could represent important independent patient-correlated factors associated with the prognosis of various cancers.[19,20]

Among these inflammatory markers, elevated serum CRP levels could indicate that the acute-stage inflammatory response is induced by hepatocytes and regulated by systemic inflammatory cytokines, especially IL-6.[21] Maeda et al demonstrated that IL-6 may be an important regulator of invasion in HCC.[22] Moreover, elevation of CRP levels is accompanied by malnutrition, leading to increased mortality in patients with cancer.[23] In addition, neutrophilia may promote VEGF release and the progression of cancer. A reduced number of lymphocytes also reflect impairment of host antitumor immunity.[24]

TABLE 1 The prognostic value of pretreatment inflammatory factors for overall survival identified by univariate and multivariate analyses in hepatocellular carcinoma patients

Variables	n	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender					
Male	141	0.965 (0.682-1.357)	.832		
Female	31				
Age (y)					
<65	115	1.047 (0.803-1.373)	.732		
≥65	57				
Liver cirrhosis					
Presence	142	1.325 (0.949-2.044)	.1002		
Absence	30				
Number of tumors					
1	109	0.865 (0.657-1.112)	.196		
≥2	63				
Tumor size (cm)					
≤5	106	1.378 (1.118-1.898)	.008	1.561 (1.256-1.941)	.006
>5	66				
Child-Pugh grade					
A	109	1.103 (0.849-1.433)	.001		
B	63				
AFP (ng/mL)					
≤400	135	1.478 (1.081-2.01)	0.03		
>400	37				
Portal vein thrombosis					
Yes	46	1.819 (1.532-3.101)	.001	1.712 (1.420-2.062)	.001
No	126				
GPS					
0	63	1.511 (1.167-2.123)	.004	1.757 (1.604-1.925)	.01
1-2	109				
C-reactive protein (CRP, mg/l)					
≤10.0	111	1.073 (0.815-1.424)	.614		
>10.0	61				
Alb (g/L)					
≥35.0	91	0.984 (0.763-1.267)	.899		
<35.0	81				
Neutrophil to lymphocyte ratio					
≤2.205	84	1.611 (1.289-2.141)	.002	1.912 (1.713-2.134)	.003
>2.205	88				
Platelet to lymphocyte ratio					
≤98.87	100	0.916 (0.696-1.175)	.464		
>98.87	72				
Lymphocyte to monocyte ratio					
≤2.83	80	1.314 (1.043-1.742)	.027		
>2.83	92				
CRP/Alb					

(Continues)

TABLE 1 (Continued)

Variables	n	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
≤0.275	105	1.493 (1.147-2.259)	.008	3.167 (2.588-3.876)	.001
>0.275	67				
Combination of CRP/Alb ratio and NLR					
CAR-High and NLR-High	41				
CAR-High or NLR-High	73	1.301 (1.269-1.335)	.001	1.204 (1.151-1.275)	.002
CAR-Low and NLR-Low	58	1.457 (1.398-1.524)	.002	1.625 (1.450-1.868)	.005

FIGURE 1 Comparison of the areas under the receiver operating curve (ROC) for the C-reactive protein/albumin ratio (CAR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), and neutrophil/lymphocyte ratio (NLR)
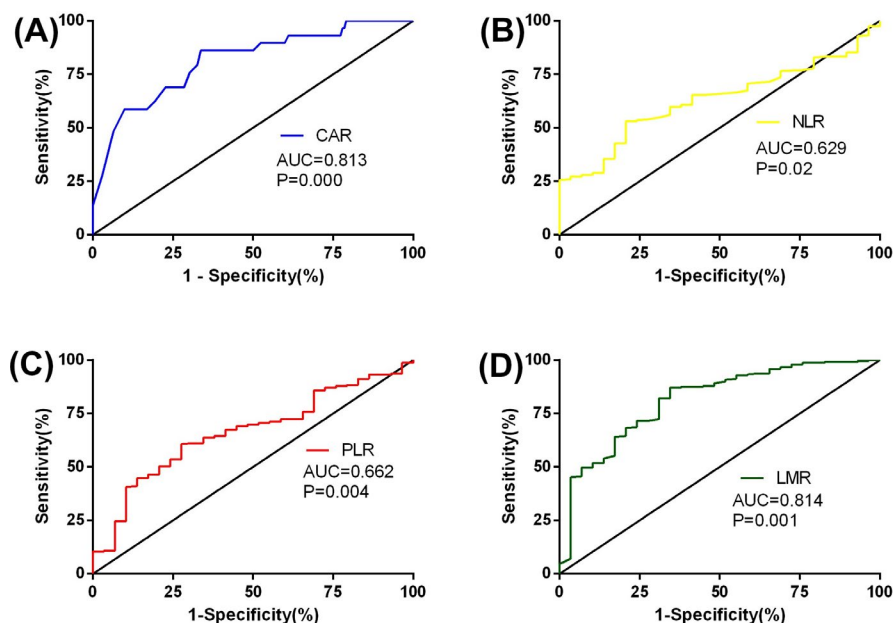
In this study, multivariate analysis revealed that the CAR, which is thought to be a low-cost prognostic inflammatory marker, as well as the GPS and the NLR were markedly associated with the prognosis of malignant tumors in patients with HCC. Akiyoshi Kinoshita et al also reported that the CAR could predict recurrence after therapy.[25] When the CAR and NLR were combined, the lowest OS rate was found for patients with HCC in the CAR-High and NLR-High cohort. These results further support that HCC is associated with the SIR and malnutrition, with subsequent poor survival rates.

Our results indicated that combining the CAR with the NLR was a useful index. Based on the ROC curve analysis, the AUC of the combined CAR and NLR was larger than those of either the CAR or NLR alone. These findings further indicated that a positive relationship exists between the CAR and NLR with respect to predicting the prognosis. The combination of the CAR and the NLR, which are based on inflammatory biomarkers, was more useful for the prediction of the prognosis of patients with HCC than either the CAR or the NLR alone.[12,26] In addition, this conclusion demonstrated that
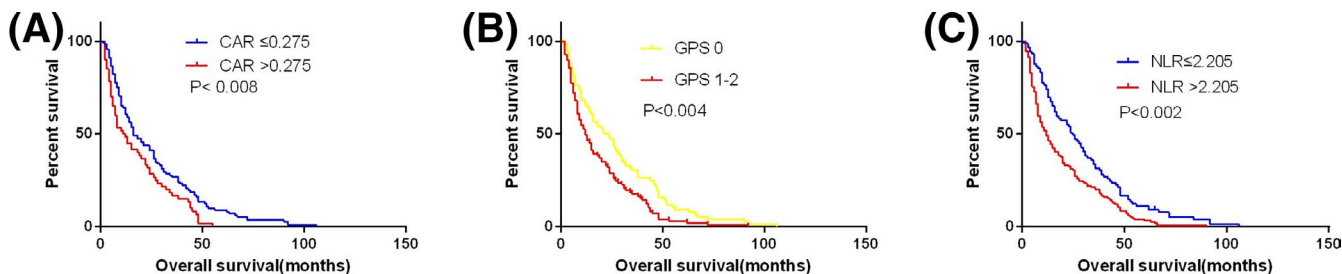
FIGURE 2 Overall survival curves based on the C-reactive protein/albumin ratio (CAR) (A), Glasgow Prognostic Score (B), and neutrophil/lymphocyte ratio (NLR) (C)

|	GPS				CAR			
Variables	0	1-2	$\chi 2$	P	≤0.275	>0.275	$\chi 2$	P
Gender								
Male	55	86	1.908	.167	86	55	0.001	.975
Female	8	23			19	12		
Age (y)								
<65	38	77	1.921	.166	65	50	2.988	.084
≥65	25	32			40	17		
Liver cirrhosis								
Presence	45	97	8.552	.003	83	59	2.307	.129
Absence	18	12			22	8		
Number of tumors								
1	47	62	5.402	.02	72	37	0.146	.702
≥2	16	47			33	30		
Tumor size(cm)								
≤5	40	66	0.146	.702	72	34	5.496	.019
>5	23	43			33	33		
Child-Pugh grade								
A	60	49	43.49	.001	72	37	3.139	.076
B	3	60			33	30		
AFP(ng/mL)								
≤400	50	85	0.045	.932	88	47	4.52	.033
>400	13	24			17	20		
Portal vein thrombosis								
Yes	14	32	1.038	.308	20	26	8.15	.004
No	49	77			85	41		
Neutrophil to lymphocyte ratio								
≤2.205	29	55	0.313	.576	58	26	4.42	.036
>2.205	34	54			47	41		
Platelet to lymphocyte ratio								
≤98.87	28	72	7.661	.006	63	37	0.383	.536
>98.87	35	37			42	30		
Lymphocyte to monocyte ratio								
≤2.83	22	58	5.369	.021	38	42	11.542	.001
>2.83	41	51			67	25		
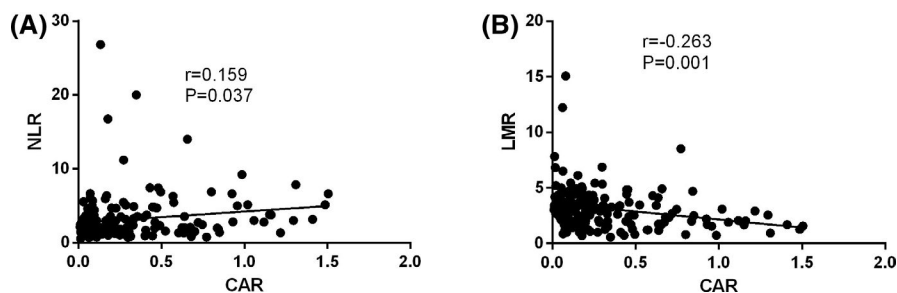
FIGURE 3 Correlation between the C-reactive protein/albumin ratio (CAR) and neutrophil/lymphocyte ratio (NLR) in hepatocellular carcinoma patients

integration of the CAR and NLR, which are classified as patient-related prognostic factors, allows effective prediction of the HCC prognosis.

There were several limitations of our study. First, because of our study was retrospective, bias may have been unavoidable. In particular, most patients participated in this study from January 2009 to
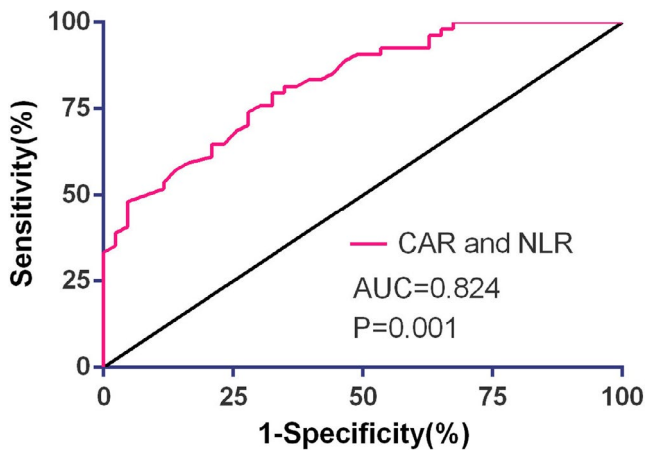
FIGURE 4 ROC curves of the combination of both the C-reactive protein/albumin ratio (CAR) and neutrophil/lymphocyte ratio (NLR) for predicting survival status

FIGURE 5 Overall survival curves based on combining both the C-reactive protein/albumin ratio (CAR) and the neutrophil/lymphocyte ratio (NLR)

March 2017. (8 years) Second, our study was a single-center study, and the number of included patients was small. Third, the cutoff values for the CAR and the LNR were 0.275 and 2.205 in the current study, respectively; in another study, Kinoshita A et al[25] used 0.037 and 1.85, respectively. The differences in these cutoff values can be partly attributed to accompanying liver cirrhosis in patients with HCC in our cohort.[25,27] Hence, our results need to be confirmed in future large-sized, randomized, controlled validation studies.

In addition to demonstrating the prognostic ability of inflammation-related factors, we associated the GPS and the CAR with clinicopathological factors in our study and revealed that the CAR is related to liver cirrhosis (P = .003), the tumor number (P = .02), the Child-Pugh grade (P = .001), the PLR (P = .006), and the LMR (P = .021). In addition, the results also demonstrated that the CAR was markedly significantly related to tumor size (P = .19), the AFP level (P = .033), the presence of portal vein thrombosis (P = .004), the NLR (P = .036), and the LMR (P = .001). There are several generally accepted explanations for these results. (a) Albumin is associated with patient nutritional status.[25] (b) Serum CRP levels are associated with the growth or invasion of tumors in various cancers, including HCC.[21,22] (c) Neutrophilia can promote the release of VEGF. Lymphocytopenia also reflects an impairment in host antitumor immunity.[24] In addition, platelets can prompt the secretion of several types of growth factors, such as tumor growth factor-beta and VEGF.[28]

Although the GPS and the CAR utilize the same factors, the CAR predicts the prognosis of HCC more accurately than the GPS because it is a continuous variable. Moreover, Kinoshita has suggested that the GPS could misestimate the prognostic ability of inflammation-related factors, as it scores CRP and serum Alb values separately.[25] In contrast, the CAR is defined as the ratio of the CRP and serum Alb levels, thus reducing the potential for overestimating or underestimating the prognostic ability of the individual markers in patients with HCC. Furthe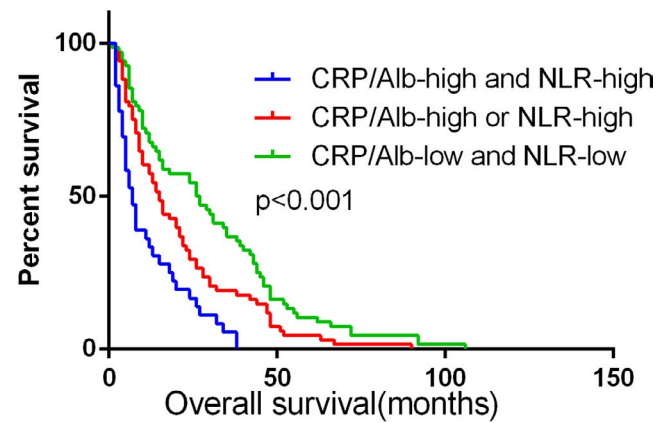rmore, the CAR has a much stronger prognostic ability than the GPS in pancreatic cancer [26,29] and patients with HCC.[25]

In summary, our study showed that the CAR is a simple, accurate, inexpensive, and convenient predictor of the prognosis of patients with HCC. Moreover, combining the NLR and the CAR results in a convenient, quick, and noninvasive biological marker that can effectively predict the prognosis of patients with HCC.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Yanjun Shen and Huige Wang contributed equally to this study.

ORCID

Jinglong Chen https://orcid.org/0000-0002-5767-823X

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