ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2024 January 15; 16(1): 1-250

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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Production Editor: *Xiang-Di Zhang*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jia-Ru Fan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
January 15, 2024

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World J Gastrointest Oncol 2024 January 15; 16(1): 61-78

DOI: 10.4251/wjgo.v16.i1.61

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Study

C-reactive protein to albumin ratio predict responses to programmed cell death-1 inhibitors in hepatocellular carcinoma patients

Bai-Bei Li, Lei-Jie Chen, Shi-Liu Lu, Biao Lei, Gui-Lin Yu, Shui-Ping Yu

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Elsayed MO, United Kingdom; van Leeuwen DJ, United States

Received: August 19, 2023
Peer-review started: August 19, 2023
First decision: October 9, 2023
Revised: October 26, 2023
Accepted: December 11, 2023
Article in press: December 11, 2023
Published online: January 15, 2024

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Abstract

BACKGROUND

Over the years, programmed cell death-1 (PD-1) inhibitors have been routinely used for hepatocellular carcinoma (HCC) treatment and yielded improved survival outcomes. Nonetheless, significant heterogeneity surrounds the outcomes of most studies. Therefore, it is critical to search for biomarkers that predict the efficacy of PD-1 inhibitors in patients with HCC.

AIM

To investigate the role of the C-reactive protein to albumin ratio (CAR) in evaluating the efficacy of PD-1 inhibitors for HCC.

METHODS

The clinical data of 160 patients with HCC treated with PD-1 inhibitors from January 2018 to November 2022 at the First Affiliated Hospital of Guangxi Medical University were retrospectively analyzed.

RESULTS

The optimal cut-off value for CAR based on progression-free survival (PFS) was determined to be 1.20 using x-tile software. Cox proportional risk model was used to determine the factors affecting prognosis. Eastern Cooperative Oncology Group performance status [hazard ratio (HR) = 1.754, 95% confidence interval (95%CI) = 1.045-2.944, *P* = 0.033], CAR (HR = 2.118, 95%CI = 1.057-4.243, *P* = 0.034) and tumor number (HR = 2.932, 95%CI = 1.246-6.897, *P* = 0.014) were independent prognostic factors for overall survival. CAR (HR = 2.730, 95%CI = 1.502-4.961, *P* = 0.001), tumor number (HR = 1.584, 95%CI = 1.003-2.500, *P* = 0.048) and neutrophil to lymphocyte ratio (HR = 1.120, 95%CI = 1.022-1.228, *P* = 0.015) were independent prognostic factors for PFS. Two nomograms were constructed based on independent prognostic factors. The C-index index and calibration plots confirmed that the nomogram is a reliable risk prediction tool. The ROC curve and decision curve analysis confirmed that the nomogram has a good predictive effect as well as a net clinical benefit.

CONCLUSION

Overall, we reveal that the CAR is a potential predictor of short- and long-term prognosis in patients with HCC treated with PD-1 inhibitors. If further verified, CAR-based nomogram may increase the number of markers that predict individualized prognosis.

Key Words: C-reactive protein to albumin ratio; Hepatocellular carcinoma; Programmed cell death-1 inhibitors; Prognosis; Nomogram

Core Tip: This study suggests that the ratio of C-reactive protein to albumin (CAR), already studied as prognosticator in other malignancies may also have a useful role to predict the outcome of hepatocellular carcinoma (HCC). Our study found that higher CAR levels are associated with poor prognosis in patients with HCC treated with programmed cell death-1 inhibitors. Nomogram based on CAR can also be used for prognostic risk stratification.

Citation: Li BB, Chen LJ, Lu SL, Lei B, Yu GL, Yu SP. C-reactive protein to albumin ratio predict responses to programmed cell death-1 inhibitors in hepatocellular carcinoma patients. *World J Gastrointest Oncol* 2024; 16(1): 61-78
URL: https://www.wjgnet.com/1948-5204/full/v16/i1/61.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i1.61

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common and difficult-to-treat cancers worldwide[1]. According to the Global Cancer Statistics 2020, HCC ranks sixth in incidence and third in mortality among all cancers, with annually approximately 906000 newly diagnosed cases and 830000 deaths annually[2]. Given the lack of specific symptoms and rapid progression, most patients with HCC are diagnosed at an advanced stage[3]. Late diagnosis, limited therapeutic options and l high recurrence rate are the main reasons for the poor prognosis of HCC[4-6].

In recent years, immunotherapy for HCC at immune checkpoints has made remarkable progress, especially antibodies targeting programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) pathway have promoted the development of systemic comprehensive therapy for HCC[7-10]. Immune checkpoint blockers targeting PD-1 have been approved for systemic integrative treatment of HCC with favorable clinical responses and survival benefits[11,12]. However, because the efficacy of PD-1 inhibitors varies widely among individuals, only a small percentage of patients benefit from anti-PD-1 therapy[13]. In clinical trials using Nivolumab and Pembrolizumab alone to treat patients with advanced HCC, the objective effective rate was only 17% to 20%[11,14]. Moreover, Pembrolizumab's phase III trial failed to reach its main endpoint, suggesting the need to identify subgroups of patients most likely to benefit from PD-1 inhibitors[15]. Immune checkpoint inhibitors are also extremely costly agents. Therefore, finding practical and robust prognostic predictors to identify HCC patients who may benefit from PD-1 therapy has recently become a research hotspot.

To date, the biomarkers that have been widely studied to predict the response of PD-1 inhibitors and improve the prognosis of tumor patients are tumor mutation load (TMB) and targeted PD-L1 expression[16-18]. Many studies have demonstrated that TMB sequencing by a polygenic cancer panel or whole exome can predict the efficacy of PD-1 inhibitor therapy in patients with multiple types of cancer, but there is little data on TMB being meaningful in patients with HCC [19,20]. The expression level of PD-L1 has been proved to be a stratification factor for random grouping of various cancer types or a selective marker for immuno-oncology subgroup analysis[21,22].The expression level of PD-L1 affects the function of T cells in tumor microenvironment, which is related to the prognosis of patients with HCC[14,23]. However, because the detection of PD-L1 expression level is expensive, PD-L1 expression level as a marker has not been widely used in clinical practice. Recent studies have shown that the increase of inflammatory characteristics in HCC tumors is

associated with improved response and overall survival (OS)[24]. As peripheral blood T cells and tumor infiltrating lymphocytes have been found to be related to the efficacy of tumor patients treated with PD-1 inhibitors[25,26]. More and more studies have begun to explore the predictive value of biomarkers derived from peripheral blood, because these biomarkers are universal, economical, fast, efficient and so on[27,28].

Many studies have found that systemic inflammatory responses affect the occurrence and development of malignant tumors by regulating the biological microenvironment[29-33]. Based on this concept, several simple and stable inflammatory markers have been shown to be associated with prognosis in malignancy, including platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index, neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index and Glasgow Prognostic Score[34-38]. Recently, a novel inflammatory marker, the C-reactive protein (CRP) to albumin ratio (CAR), has been reported as an independent prognostic factor in various malignancies. Ren *et al*[39] reported that CAR predicted mortality and recurrence rates after resection of HCC. Huang *et al*[40] reported that the CAR could predict the outcomes of patients with nasopharyngeal carcinoma treated with chemotherapy. Based on the prognostic role of CAR in patients with other malignant tumors, we speculate that CAR may be related to the prognosis of HCC patients treated with PD-1 inhibitors. However, the role of the CAR in HCC patients treated with PD-1 inhibitors has not been evaluated. Therefore, we conducted this study.

The present study assessed the prognostic performance of the CAR in HCC patients treated with PD-1 inhibitors. We also constructed nomogram models based on the results of Cox multifactorial analysis for prognostic prediction of OS and progression-free survival (PFS) in HCC patients treated with PD-1 inhibitors.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of patients with HCC who received PD-1 inhibitors in the first affiliated Hospital of Guangxi Medical University from January 2018 to November 2022. The inclusion criteria for this study were as follows: (1) Aged at least 18 at diagnosis; (2) clinical or pathological diagnosis of HCC; (3) treatment with PD-1 inhibitors for at least 3 cycles; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1; and (5) child-Pugh Class A or B. We initially enrolled 213 patients in the study. The exclusion criteria were as follows: (1) Diagnosis of secondary liver malignancy or mixed liver malignancy; (2) treatment with PD-1 inhibitors < 3 cycles; (3) child-Pugh Class C; (4) severe immune-related disease; (5) incomplete baseline data or follow-up information; and (6) suffer from inflammatory disease or blood system disease. Fifty-three patients were excluded, and 160 patients with HCC were finally included for analysis.

PD-1 blockers were administered intravenously at standard doses: Sintilimab 200mg per 2 wk; toripalimab at 3 mg/kg body weight per 2 wk; tislelizumab at 200 mg per 3 wk; and camrelizumab at 3 mg/kg body weight per 3 wk. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events v5.0. Patients were treated according to the treatment plan until disease progression (PD) or AEs occurred.

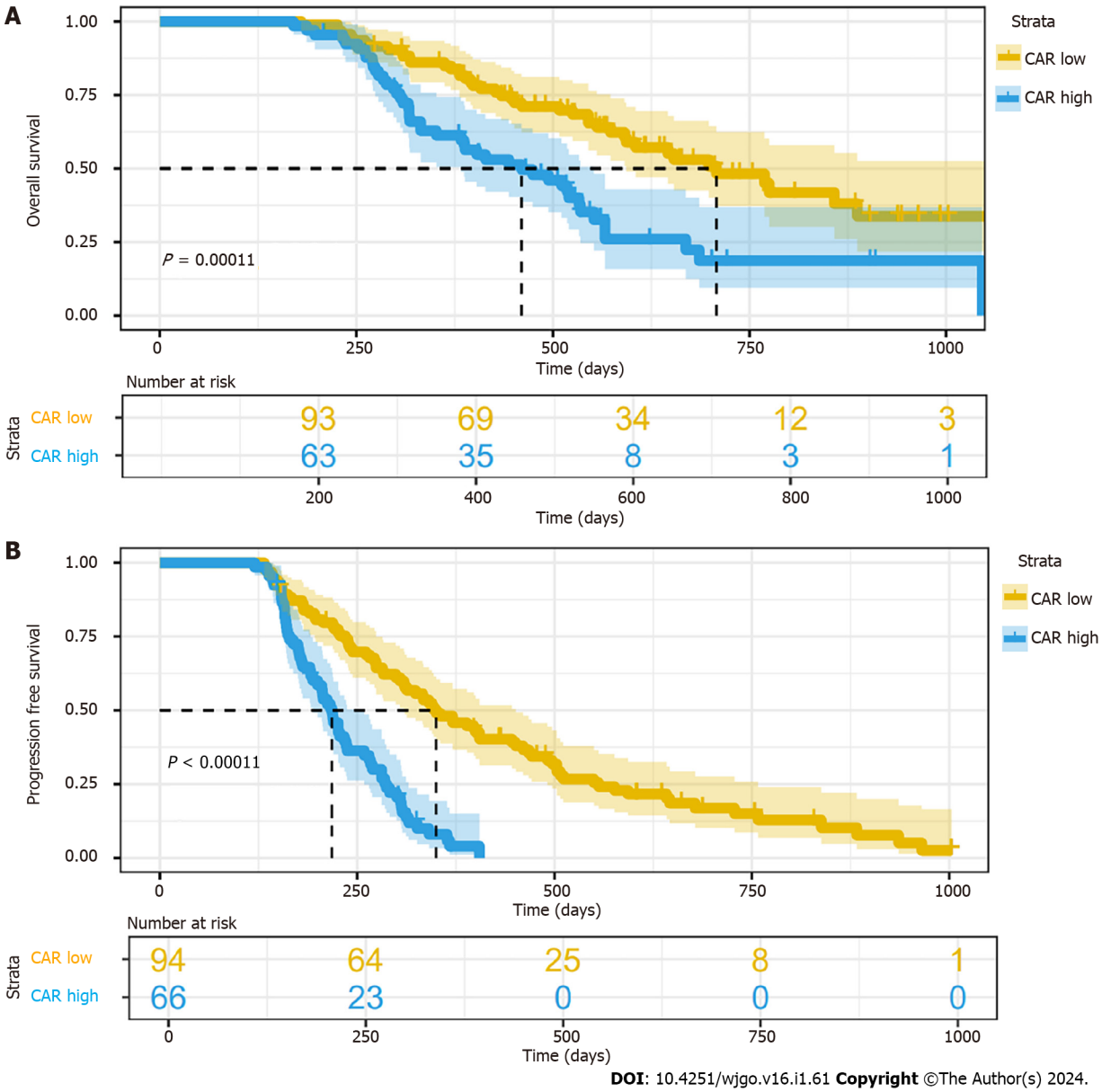
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2023-E332-01).

Data collection

All data, including basic patient information, treatment strategy, laboratory test results and device results, were obtained from the electronic medical records and follow-up by phone calls. Serologic results measured within 5 d prior to the patient's first PD-1 inhibitor treatment were selected. Radiographic response was assessed by computed tomography or magnetic resonance imaging approximately every 6-12 wk after the start of treatment. Follow-up was performed by phone call every 2 mo after the start of treatment. The final data collected included age, gender, history of hepatitis virus, Child-Pugh, laboratory test results, ECOG PS, tumor size, tumor number, macrovascular invasion, extrahepatic metastases, prior medical history, history of smoking, history of alcohol consumption, Barcelona Clinic Liver Cancer (BCLC) stage, previous treatment, and survival data. The Child-Pugh classification was assessed according to ascites, hepatic encephalopathy, albumin, bilirubin and prothrombin time. The CAR was obtained by dividing the CRP (mg/L) by albumin (g/L). The remaining ratios were obtained as follows: PLR = platelets (10^9/L)/lymphocytes (10^9/L); lymphocyte to CRP ratio (LCR) = lymphocytes (10^9/L)/CRP(mg/L); NLR = neutrophils (10^9/L)/lymphocytes (10^9/L). PFS was defined as the time from initiation of PD-1 inhibitors to recurrence of HCC, PD, or death of the patient from HCC. OS was defined from initiation of PD-1 therapy until death.

Statistical analysis

R software (version 4.2.2) and SPSS (version 26) were used for statistical analyses. X-tile software was used to obtain the best cut-off values for continuous variables. Continuous variables were analyzed using *t*-tests or non-parametric tests, and categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. Univariate and multivariate Cox regression analysis were used to determine the independent predictor variables for PFS and OS. The risk-stratified survival curves were expressed as Kaplan-Meier curves and analyzed using Log-rank tests. The nomogram and calibration plots were plotted using the "rms" package, the C-Index was calculated using the "survcomp" package, and the ROC curves were plotted using the "pROC" package. For all tests, a two-sided $P < 0.05$ was considered statistically significant.



DOI: 10.4251/wjgo.v16.i1.61

Figure 1 Kaplan-Meier survival curve of hepatocellular carcinoma in low C-reactive protein to albumin ratio group and high C-reactive protein to albumin group. A: Overall survival; B: Progression-free survival. CAR: C-reactive protein to albumin ratio.

RESULTS

Patient characteristics

The characteristics of HCC patients included in this study are shown in Table 1. A total of 160 patients were included in this study, including 134 males (83.8%) and 26 females (16.3%).Thirty-nine (24.4%) patients were older than 60 years; 131 (81.9%) had previous hepatitis virus infection; 85 (53.1%) had cirrhosis; 121 (75.6%) had multiple tumors; 71 (44.4%) had tumor invasion of the portal vein; and 83 (51.9%) had extrahepatic metastasis of the tumor. According to BCLC staging, most patients presented with BCLC C (n = 120, 75.0%), followed by BCLC B (n = 30, 18.8%) and BCLC A (n = 10, 6.3%). Using X-tile software, the best cut-off value of CAR was determined to be 1.20 according to PFS. Based on this cut-off value, patients were included in the low CAR group (n = 94) and high CAR group (n = 66). The correlation analysis of clinicopathological factors with CAR is shown in Table 1. CAR was associated with gender (P = 0.045), macroscopic vascular invasion (P = 0.013) and smoking history (P = 0.013). There was no significant correlation between CAR and age, hepatitis infection, Child-Pugh grade, alpha-fetoprotein level, ECOG PS, tumor size, tumor number, extrahepatic metastasis, diabetes, hypertension, alcohol drinking, cirrhosis, previous ablation, previous transcatheter arterial chemoembolization (TACE), previous surgery and BCLC stage (P > 0.05).

Comparison of low and high CAR survival curves

The median overall survival was 466 d and the median PFS was 168 d. A total of 88 patients (55%) died and 140 (87.5%) had confirmed programmed death at the last follow-up visit. The Kaplan-Meier method and log-rank test were used to

Table 1 The correlations between the C-reactive protein to albumin ratio and clinicopathological factors, *n* (%)

	CAR ≤ 1.20 (*n* = 94)	CAR > 1.20 (*n* = 66)	Total (*n* = 160)	*P* value
Age (yr)				0.143
≤ 60	75 (79.8)	46 (69.7)	121 (75.6)	
> 60	19 (20.2)	20 (30.3)	39 (24.4)	
Gender				0.045
Male	77 (81.9)	57 (86.4)	134 (83.8)	
Female	17 (18.1)	9 (13.6)	26 (16.3)	
Hepatitis infection				0.988
No	17 (18.1)	12 (18.2)	29 (18.1)	
Yes	77 (81.9)	54 (81.8)	131 (81.9)	
Child-Pugh grade				0.749
A	75 (79.8)	54 (81.8)	129 (80.6)	
B	19 (21.2)	12 (18.2)	31 (19.4)	
AFP level (ng/L)				0.365
≤ 400	58 (61.7)	36 (54.5)	94 (58.8)	
> 400	36 (38.3)	30 (45.5)	66 (41.3)	
ECOG PS				0.990
0	30 (31.9)	21 (31.8)	51 (31.9)	
≥ 1	64 (68.1)	45 (68.2)	109 (68.1)	
Tumor size (cm)				0.248
≤ 5	26 (27.7)	13 (19.7)	39 (24.4)	
> 5	68 (72.3)	53 (80.3)	121 (75.6)	
Tumor number				0.512
Single	18 (19.1)	10 (15.2)	28 (17.5)	
Multiple	76 (80.9)	56 (84.8)	132 (82.5)	
Macroscopic vascular invasion				0.013
Absent	60 (63.8)	29 (43.9)	89 (55.6)	
Present	34 (36.2)	37 (56.1)	71 (44.4)	
Extrahepatic metastasis				0.173
Absent	41 (43.6)	36 (54.5)	77 (48.1)	
Present	53 (56.4)	30 (45.5)	83 (51.9)	
Diabetes				0.955
No	84 (89.4)	59 (89.4)	143 (89.4)	
Yes	10 (10.6)	7 (10.6)	17 (10.6)	
Hypertension				0.455
No	81 (86.2)	54 (81.8)	135 (84.4)	
Yes	13 (13.8)	12 (18.2)	25 (15.6)	
Smoke				0.013
No	60 (63.8)	29 (43.9)	89 (55.6)	
Yes	34 (36.2)	37 (56.1)	71 (44.4)	
Drink				0.364
No	51 (54.3)	31 (47.0)	82 (51.2)	

Yes	43 (45.7)	35 (53.0)	78 (48.8)	
Cirrhosis				0.191
No	40 (42.6)	35 (53.0)	75 (46.9)	
Yes	54 (57.4)	31 (47.0)	85 (53.1)	
Previous Ablation				0.119
No	87 (92.6)	56 (84.8)	143 (89.4)	
Yes	7 (7.4)	10 (15.2)	17 (10.6)	
Previous TACE				0.505
No	52 (55.3)	40 (60.6)	92 (57.)	
Yes	42 (44.7)	26 (39.4)	68 (42.5)	
Previous Surgery				0.701
No	57 (60.6)	42 (63.6)	99 (61.9)	
Yes	37 (39.4)	24 (36.4)	61 (38.1)	
BCLC stage				0.966
A	6 (6.4)	4 (6.1)	10 (6.3)	
B	17 (18.1)	13 (19.7)	30 (18.8)	
C	71 (75.5)	49 (74.2)	120 (75.0)	

AFP: Alpha-fetoprotein; ECOG PS: Eastern Cooperative Oncology Group performance status; CAR: C-reactive protein to albumin ratio; TACE: Transcatheter arterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer.

compare the survival curves between the low and high CAR groups (Figure 1). The results showed that OS was significantly shorter in patients with high CAR compared to those with low CAR ($P < 0.001$). Similarly, PFS was significantly worse in patients with high CAR compared to patients with low CAR ($P < 0.001$).

Correlation of CAR with patient survival

Multiple clinicopathological factors were included in the Cox proportional hazards model for survival analysis. Univariate Cox regression analysis showed that ECOG PS ($P = 0.005$), protein induced by vitamin K absence II ($P = 0.014$), CAR ($P = 0.000$), tumor size ($P = 0.002$), tumor number ($P = 0.004$), macrovascular invasion ($P = 0.042$), smoke ($P = 0.024$), previous operation ($P = 0.012$), CRP ($P = 0.005$), albumin ($P = 0.013$), and aspartate aminotransferase ($P = 0.000$) were significantly correlated with OS. However, during multivariate Cox regression analysis, only ECOG PS [hazard ratio (HR) = 1.754, 95% confidence interval (95%CI) = 1.045-2.94, $P = 0.033$], high CAR (HR = 2.118, 95%CI = 1.057-4.243, $P = 0.034$) and multiple tumor number (HR = 2.932, 95%CI = 1.246-6.897, $P = 0.014$) were the independent factors affecting the prognosis of OS (Table 2). Similarly, univariate Cox regression analysis showed that CAR ($P = 0.000$), Tumor number ($P = 0.028$), CRP ($P = 0.000$), albumin ($P = 0.004$), LCR ($P = 0.026$), NLR ($P = 0.036$) were significantly associated with PFS. Multivariate Cox regression analysis showed that high CAR (HR = 2.730, 95%CI = 1.502-4.961, $P = 0.001$), multiple tumor number (HR = 1.584, 95%CI = 1.003-2.500, $P = 0.048$) and NLR (HR = 1.120, 95%CI = 1.022-1.228, $P = 0.015$) were independent predictors of PFS (Table 3).

Establishment and validation of OS nomogram

Based on the results of multivariate Cox regression, a nomogram was established based on CAR, ECOG PS and tumor number to predict the OS of patients with HCC treated with PD-1 inhibitors. The nomogram was used to estimate the overall survival of patients with HCC at 12, 18 and 24 mo by calculating the sum of the factor scores (Figure 2A). Then, the prediction ability of the nomogram was verified by the concordance index (C-index), receiver operating characteristic (ROC) curve, calibration plot and decision curve analysis (DCA). The C-index of OS nomogram was 0.721 (95%CI: 0.573-0.832). The nomogram predicted an area under the ROC curve (AUC) of 0.696 for 12-mo OS, 0.765 for 18-mo OS, and 0.735 for 24-mo OS (Figure 3A). In addition, the calibration plots show the best agreement between the nomogram and the actual observations (Figure 4A). DCA revealed that the nomogram model provided a high clinical net benefit for predicting OS at 360, 540 and 720 d (Figure 5A).

Establishment and validation of PFS nomogram

CAR, NLR and tumor number were identified as independent prognostic factors for PFS by multifactorial Cox regression analysis. Independent prognostic factors were incorporated to create a nomogram to predict PFS in patients with HCC (Figure 2B). The C-index of the PFS nomogram was 0.665 (95%CI: 0.552- 0.762). The AUC was used to measure the performance of the PFS nomogram model. The AUC was 0.741, 0.787 and 0.804 for predicting the PFS at 9, 12 and 15 mo

Table 2 Univariate and multivariate Cox regression analyses of risk factors for overall survival

	Univariate HR (95%CI)	*P* value	Multivariate HR (95%CI)	*P* value
Age (yr)				
≤ 60	1.0			
> 60	1.222 (0.763-1.958)	0.403		
Gender				
Male	1.0			
Female	1.127 (0.669-1.898)	0.653		
Aetiology				
Other	1.0			
Viral hepatitis	1.464 (0.810-2.646)	0.207		
ECOG PS				
0	1.0			
≥ 1	2.010 (1.229-3.288)	0.005	1.754 (1.045-2.944)	0.033
Child-Pugh grade				
A	1.0			
B	1.348 (0.798-2.276)	0.264		
AFP (ng/mL)				
≤ 400	1.0			
> 400	1.401 (0.920-2.133)	0.116		
PIVKA-II (mAU/mL)				
≤ 100	1.0			
> 100	1.942 (1.142-3.302)	0.014		
CAR				
≤ 1.20	1.0			
> 1.20	2.264 (1.480-3.464)	0.000	2.118 (1.057-4.243)	0.034
Tumor size (cm)				
≤ 5	1.0			
> 5	2.671 (1.451-4.971)	0.002		
Tumor number				
Single	1.0			
Multiple	3.328 (1.452-7.682)	0.004	2.932 (1.246-6.897)	0.014
Extrahepatic metastasis				
-	1.0			
+	1.121 (0.735-1.709)	0.597		
Macrovascular invasion				
-	1.0			
+	1.550 (1.015-2.367)	0.042		
Diabetes				
No	1.0			
Yes	0.934 (0.467-1.868)	0.848		
Hypertension				
No	1.0			

Yes	0.902 (0.508-1.602)	0.726
Smoke		
No	1.0	
Yes	1.634 (1.068-2.501)	0.024
Drink		
No	1.0	
Yes	1.386 (0.911-2.111)	0.128
Cirrhosis		
No	1.0	
Yes	0.899 (0.589-1.372)	0.622
Previous TACE		
No	1.0	
Yes	0.897 (0.587-1.371)	0.615
Previous ablation		
No	1.0	
Yes	0.719 (0.346-1.497)	0.378
Previous operation		
No	1.0	
Yes	0.555 (0.351-0.878)	0.012
CRP (mg/L)	1.008 (1.002-1.014)	0.005
ALB (g/L)	0.944 (0.902-0.988)	0.013
AST (U/L)	1.006 (1.003-1.010)	0.000
ALT (U/L)	1.004 (0.998-1.011)	0.219
PLR	0.999 (0.997-1.002)	0.562
LCR	0.771 (0.065-9.087)	0.836
NLR	1.036 (0.953-1.126)	0.410

ECOG PS: Eastern Cooperative Oncology Group Performance Status; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence II; CAR: C-reactive protein to albumin ratio; HR: Hazard ratio; 95%CI: 95% confidence interval; TACE: Transcatheter arterial chemoembolization; CRP: C-reactive protein; ALB: Albumin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PLR: Platelet to lymphocyte ratio; LCR: Lymphocyte-C reactive protein ratio; NLR: Neutrophil to lymphocyte ratio.

(Figure 3B).The calibration plot of PFS shows a good consistency between the predicted values and the actual values (Figure 4B). The DCA curve shows a huge net benefit at different time points, indicating that nomogram has a good potential clinical validity for predicting PFS (Figure 5B).

Establishment of risk classification system

Based on the nomogram, each patient received a personalized risk score. We use the X-tile software to determine the cut-off value of the risk score (Figure 6). According to OS nomogram and cutoff value, all patients were divided into low risk (score: 0-116.32), middle risk (score: 155.96-160.36) and high risk groups (score: 216.32-216.32) according to the OS nomogram. Similarly, all patients were classified into low risk (score: 3.65-54.01), middle risk (score: 54.26-91.33) and high risk groups (score: 91.40-142.67) according to the PFS nomogram and cut-off value. The Kaplan-Meier curves showed that this risk classification system had good stratification and differentiation ability (Figure 7).

DISCUSSION

This study investigated the relationship between clinicopathological factors and prognosis in patients with HCC treated with PD-1 inhibitors. Multivariate COX regression analysis showed that CAR, tumor number and ECOG PS were independent prognostic factors for OS. CAR, tumor number and NLR were independent prognostic factors for PFS. In Kaplan-Meier survival curve analysis, OS and PFS were significantly better in the low-CAR group than in the high-CAR

Table 3 Univariate and multivariate Cox regression analyses of risk factors for progression free survival.

	Univariate HR (95%CI)	*P* value	Multivariate HR (95%CI)	*P* value
Age (yr)				
≤ 60	1.0			
> 60	1.036 (0.706-1.521)	0.856		
Gender				
Male	1.0			
Female	1.181 (0.765-1.824)	0.453		
Aetiology				
Other	1.0			
Viral hepatitis	1.535 (0.962-2.450)	0.072		
ECOG PS				
0	1.0			
≥ 1	1.258 (0.881-1.797)	0.206		
Child-Pugh grade				
A	1.0			
B	1.430 (0.926-2.208)	0.106		
AFP (ng/mL)				
≤ 400	1.0			
> 400	1.321 (0.943-1.849)	0.105		
PIVKA-II (mAU/mL)				
≤ 100	1.0			
> 100	1.013 (0.698-1.471)	0.944		
CAR				
≤ 1.20	1.0			
> 1.20	3.467 (2.342-5.132)	0.000	2.730 (1.502-4.961)	0.001
Tumor size (cm)				
≤ 5	1.0			
> 5	1.295 (0.882-1.901)	0.188		
Tumor number				
Single	1.0			
Multiple	1.653 (1.054-2.591)	0.028	1.584 (1.003-2.500)	0.048
Extrahepatic metastasis				
-	1.0			
+	1.154 (0.827-1.609)	0.400		
Macrovascular invasion				
-	1.0			
+	1.083 (0.774-1.514)	0.642		
Diabetes				
No	1.0			
Yes	0.967 (0.573-1.632)	0.900		
Hypertension				
No	1.0			

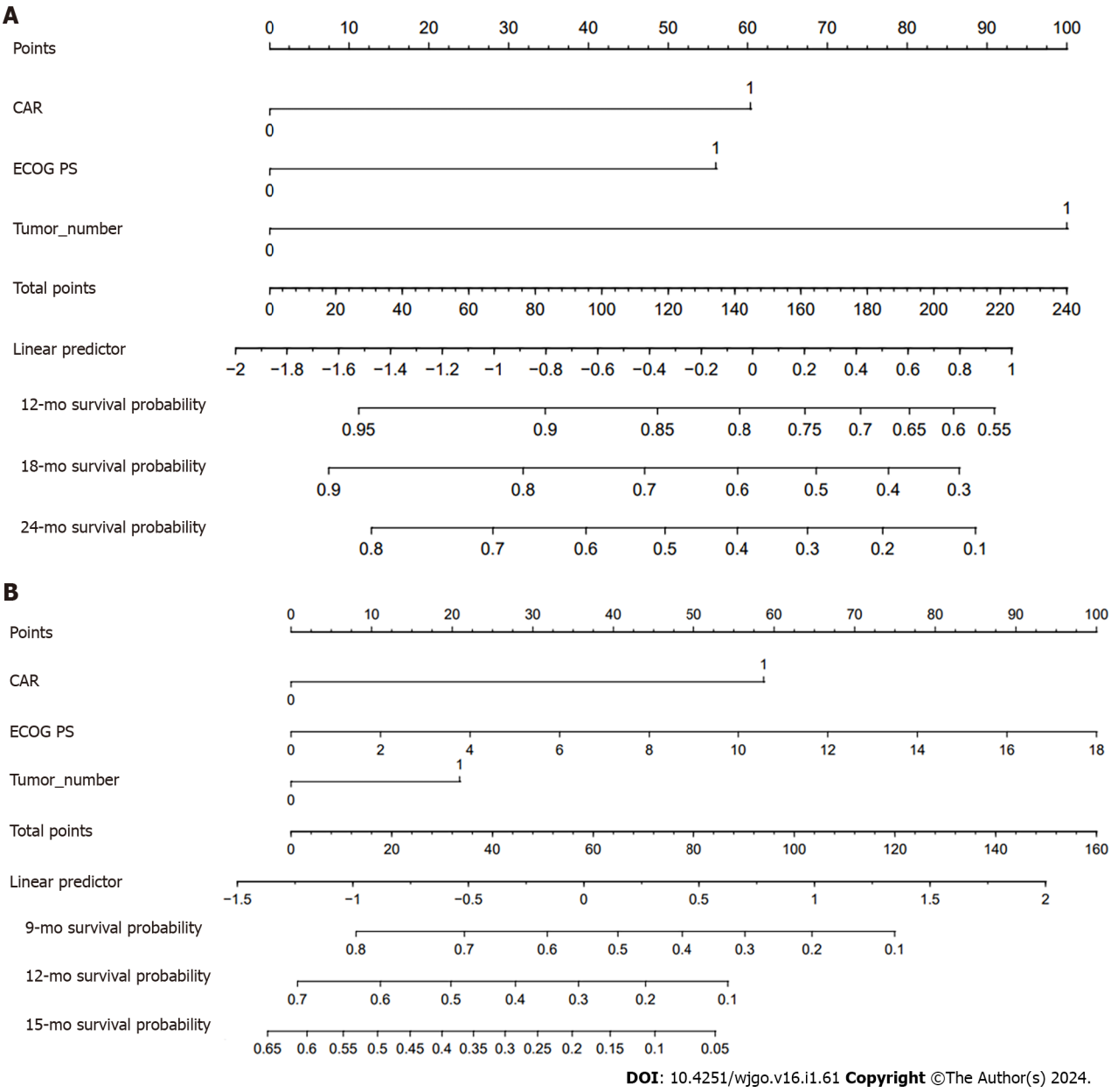
Yes	0.969 (0.613-1.530)	0.892		
Smoke				
No	1.0			
Yes	1.349 (0.962-1.892)	0.082		
Drink				
No	1.0			
Yes	1.091 (0.781-1.524)	0.609		
Cirrhosis				
No	1.0			
Yes	1.169 (0.837-1.632)	0.360		
Previous TACE				
No	1.0			
Yes	0.905 (0.646-1.267)	0.561		
Previous ablation				
No	1.0			
Yes	1.361 (0.806-2.297)	0.249		
Previous operation				
No	1.0			
Yes	1.143 (0.812-1.609)	0.442		
CRP (mg/L)	1.014 (1.008-1.019)	0.000		
ALB (g/L)	0.950 (0.918-0.983)	0.004		
AST (U/L)	1.001 (0.997-1.004)	0.771		
ALT (U/L)	0.999 (0.993-1.005)	0.643		
PLR	1.000 (0.998-1.002)	0.733		
LCR	0.064 (0.006-0.722)	0.026		
NLR	1.092 (1.006-1.186)	0.036	1.120 (1.022-1.228)	0.015

ECOG PS: Eastern Cooperative Oncology Group Performance Status; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence II; CAR: C-reactive protein to albumin ratio; HR: Hazard ratio; 95%CI: 95% confidence interval; TACE: Transcatheter arterial chemoembolization; CRP: C-reactive protein; ALB: Albumin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PLR: Platelet to lymphocyte ratio; LCR: Lymphocyte-C reactive protein ratio; NLR: Neutrophil to lymphocyte ratio.

group, which also indicated that CAR could predict patient prognosis. Previous studies have shown that CAR can be used as a prognostic factor to predict the prognosis of patients with pancreatic cancer, gallbladder cancer, non-small cell lung cancer, neck squamous cell carcinoma, and cholangiocarcinoma[41-43]. At present, the mechanism of the effect of CAR on the prognosis of HCC patients is not completely clear, but there are some possible explanations. CAR is a complex biomarker composed of CRP and albumin, which is affected by both CRP and albumin.

CRP is an acute phase protein produced after inflammation, tissue injury, malignant tumor and other changes[44]. It has been established that the CRP recognizes exogenous substances or necrotic cells, activates the complement system, and enhances phagocytosis[45]. CRPs are regulated by cytokines such as IL-1, IL-6 and tumor necrosis factor, which are co-secreted by malignant tumor cells and host immune cells and are associated with tumor growth, invasion, metastasis and chemotherapy resistance[46].Therefore, the increase of CRP may mean a poor prognosis of malignant tumors.

Albumin is synthesized by the liver, accounting for about 50% of total plasma protein, maintaining body nutrition and osmotic pressure, and is one of the main markers reflecting the nutritional status of the body[47,48]. Trauma, malignant tumors and systemic inflammatory reactions can cause a decrease in albumin synthesis by the liver, promote albumin catabolism, aggravate capillary infiltration and cause hypoproteinemia[49]. Hypoproteinemia causes decreased collagen synthesis, increased granuloma formation and hypercellularity, which suppresses the body's immune response and triggers tumor invasion and drug resistance[50-53]. Previous studies have also demonstrated that albumin is closely related to the prognosis of patients with HCC[54,55]. Compared with other tests, we have made some progress in this test. Compared with the expression of TMB and PD-L1, serum CAR not only responds to the inflammatory and immune status of the body, but also to the nutritional status of the body, which can predict the prognosis of patients with malignant tumors. Not only that, CAR can be obtained from routine blood tests with no additional medical costs.



DOI: 10.4251/wjgo.v16.i1.61

Figure 2 Nomogram models of overall survival and progression-free survival in hepatocellular carcinoma patients. A: Nomogram models of overall survival at 12, 18 and 24 mo in hepatocellular carcinoma (HCC) patients; B: Nomogram model of progression-free survival at 9, 12 and 15 mo in HCC patients. C-reactive protein to albumin ratio (CAR) = 0 means CAR ≤ 1.20, CAR = 1 means CAR > 1.20; tumor number = 0 means single tumor, tumor number = 1 means multiple tumors. CAR: C-reactive protein to albumin ratio; NLR: Neutrophil-to-lymphocyte ratio; ECOG PS: Eastern Cooperative Oncology Group performance status.

Therefore, CAR is affordable, convenient and effective for both clinicians and patients.

We also found that tumor number, ECOG PS and NLR are associated with the prognosis of patients with HCC, which is consistent with previous studies. Katayama *et al*[56] confirmed that tumor number can predict the efficacy and prognosis of patients with HCC after TACE. In a multicenter retrospective study, ECOG PS was confirmed to be a prognostic factor in patients with unresectable HCC who received PD-1 inhibitors combined with anti-angiogenic therapy [57]. A meta-analysis showed that NLR is a predictor of outcome after treatment for HCC[58].

We constructed two prognostic nomograms to predict clinical outcomes based on the independent prognostic factors determined by multivariate Cox regression analysis. The C-index index and calibration plots confirmed that our nomograms were reliable prediction tools. ROC curve confirms that OS nomogram can well predict patients' OS at 12, 18, and 24 mo, and also confirms that PFS nomogram has an advantage in predicting PFS at 9, 12, and 15 mo. In addition, we have established a new risk classification system based on nomogram to help assess the risk level of patients with HCC treated with PD-1 inhibitors, resulting in individualized treatment and accurate prognosis. Moreover, it is gratifying to note that ECOG PS is obtained by observing patients, NLR is obtained by routine blood tests, and tumor number is obtained by routine imaging tests. These markers are simple, easily accessible, non-invasive, repeatable and cost-effective, and are beneficial to the individual patients as well as the health care system.

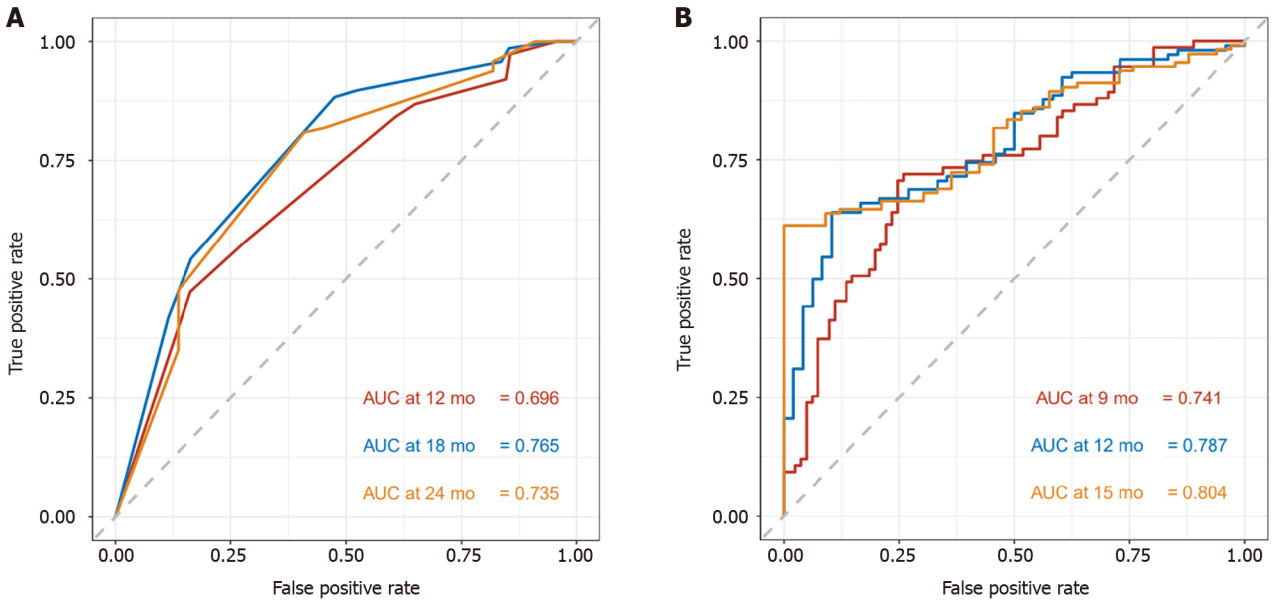


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Figure 3 The area under the receiver operating characteristic curve was utilized to weigh up the performance of overall survival and progression-free survival nomogram models. A: Receiver operating characteristic (ROC) curves for 12-mo, 18-mo, and 24-mo overall survival; B: ROC curves for 9-mo, 12-mo, and 15-mo progression-free survival. AUC: Area under the receiver operating characteristic curve.

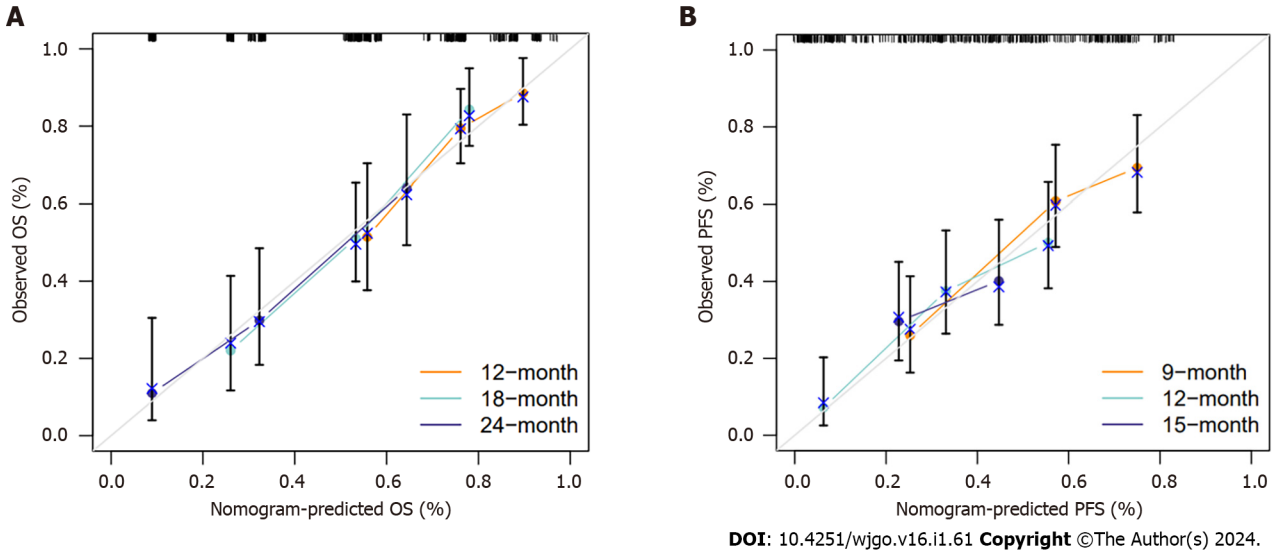

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Figure 4 Calibration curves for nomogram models related to overall survival and progression-free survival. A: Calibration curves of overall survival at 12 mo, 18 mo and 24 mo; B: Calibration curves of progression-free survival at 9 mo, 12 mo and 15 mo. OS: Overall survival; PFS: Progression-free survival.

It is worth noting that there are some limitations to our research. First of all, this is a retrospective study, and selection errors are inevitable. Secondly, only 160 cases were included in this study, and multicenter, larger sample studies are needed in the future to verify our conclusions.

CONCLUSION

In this study, the CAR was found to be a potential predictor of short- and long-term prognosis in patients with HCC treated with PD-1 inhibitors. The nomogram based on CAR achieved individualized prediction for patients.

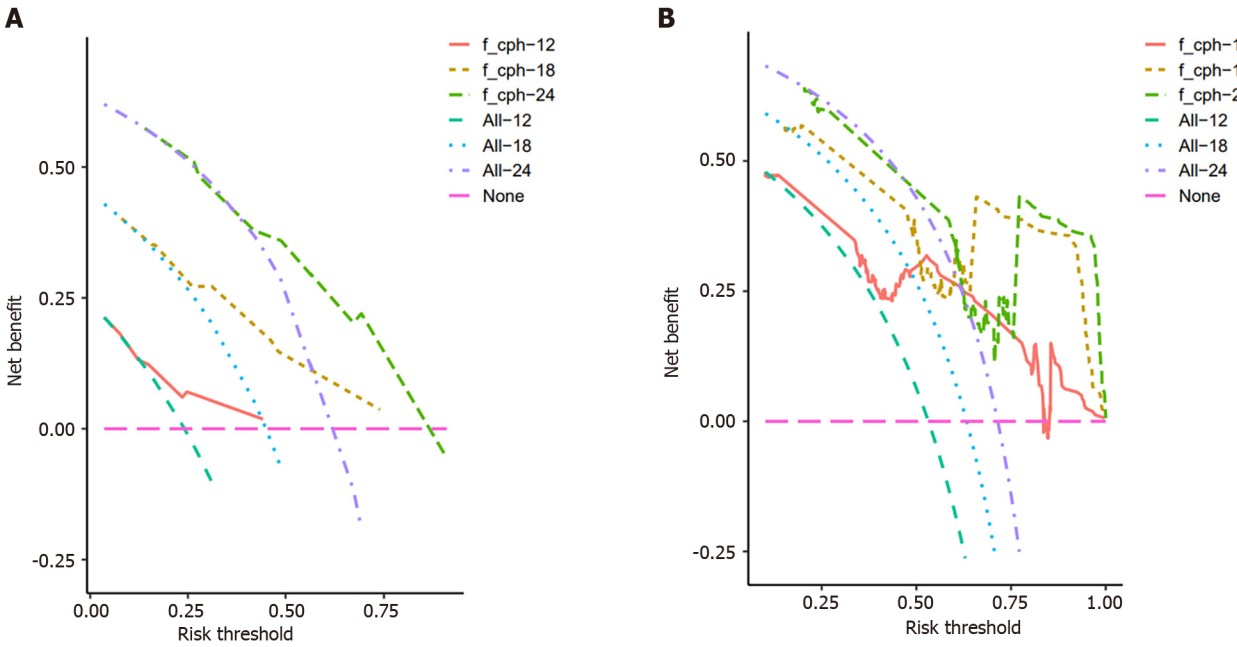

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Figure 5 Decision curve analysis of overall survival and progression-free survival nomograms. A: Decision curve analysis (DCA) of overall survival at 12, 18, and 24 mo; B: DCA of progression-free survival at 9, 12, and 15 mo.

A

Statistics

Pt No	% Total	Events	Rate	Rank	Range
53	33.13	15	28.30	0 to 4	0.00 thru 116.32
69	43.13	41	59.42	5 to 6	155.96 thru 160.36
38	23.75	32	84.21	7 to 7	216.32 thru 216.32
160	100.00	88	55.00	0 to 7	0.00 thru 216.32

Chi-Sq Hi/Mid/Lo	35.3057	Max: 35.305
Lo vs Mid	14.6321	
Mid vs Hi	7.3442	
Lo vs Hi	34.2852	
Relative Risk 1 vs 2 vs 3	1.00 / 2.10 / 2.98	

B

Statistics

Pt No	% Total	Events	Rate	Rank	Range
85	53.13	70	82.35	0 to 84	3.65 thru 54.01
39	24.38	36	92.31	85 to 123	54.26 thru 91.33
36	22.50	34	94.44	124 to 159	91.40 thru 142.67
160	100.00	140	87.50	0 to 159	3.65 thru 142.67

Chi-Sq Hi/Mid/Lo	55.9833	Max: 56.869
Lo vs Mid	27.2920	
Mid vs Hi	5.8817	
Lo vs Hi	49.3482	
Relative Risk 1 vs 2 vs 3	1.00 / 1.12 / 1.15	

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Figure 6 The X-tile software is used to determine the cut-off value of the risk score. A: The cut-off value of the overall survival nomogram risk score; B: The cut-off value of the progression-free survival nomogram risk score.

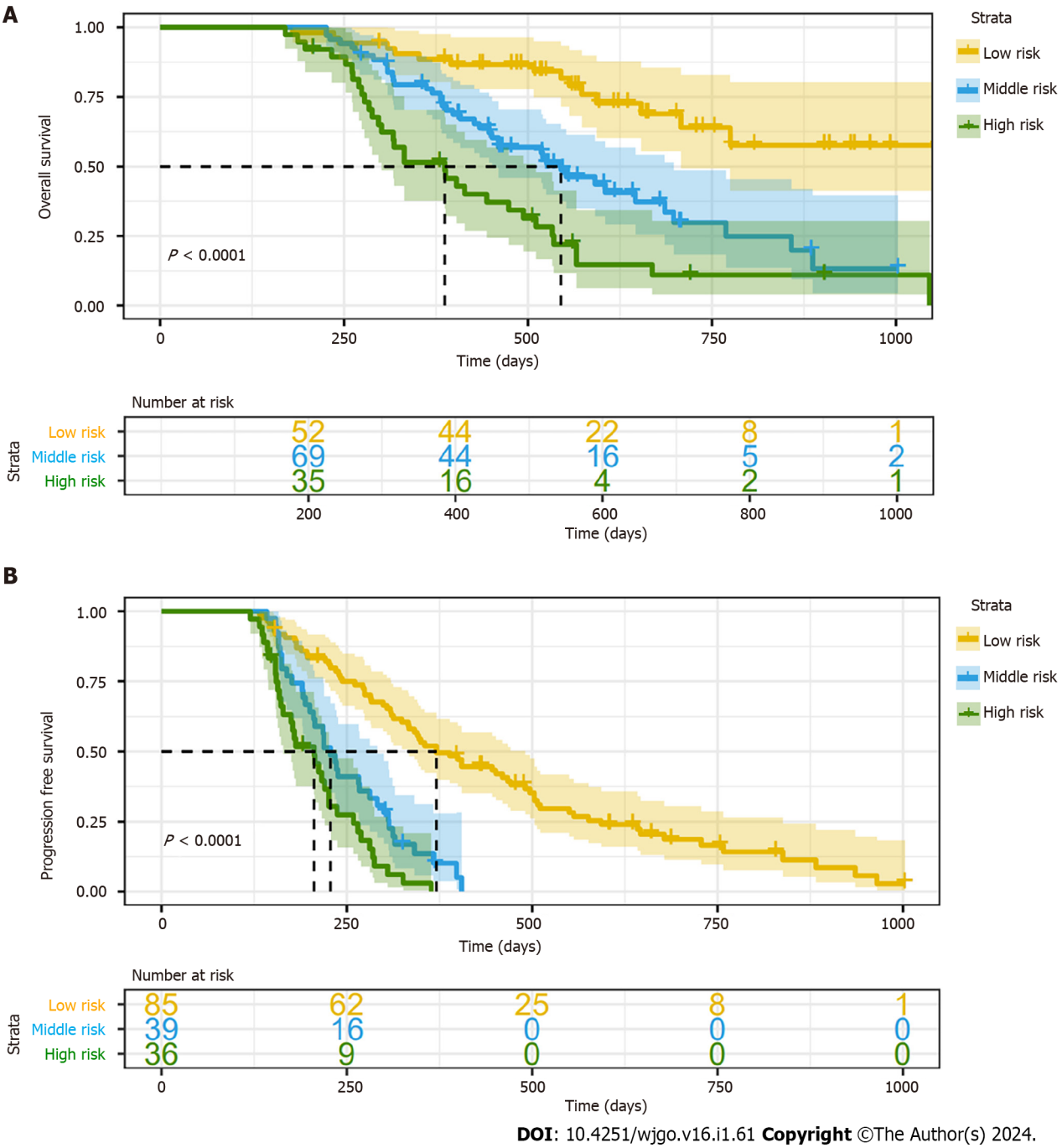

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Figure 7 Kaplan-Meier curves for risk classification system based on nomogram. A: Risk classification system of overall survival nomogram; B: Risk classification system of progression-free survival nomogram.

ARTICLE HIGHLIGHTS

Research background

Over the years, programmed cell death-1 (PD-1) inhibitors have been routinely used for hepatocellular carcinoma (HCC) treatment and yielded improved survival outcomes. Nonetheless, significant heterogeneity surrounds the outcomes of most studies. Therefore, it is critical to find biomarkers that predict the efficacy of PD-1 inhibitors in patients with HCC. This may also help in meaningful and cost-effective use of this very costly therapy.

Research motivation

The role of the C-reactive protein to albumin ratio (CAR), whose prognostic value was suggested for various other malignancies had not yet been in HCC patients treated with PD-1 inhibitors has not been evaluated.

Research objectives
This study aimed to investigate the performance of the CAR in assessing the efficacy of patients receiving PD-1 inhibitors for HCC.

Research methods
The clinical data of 160 patients with HCC treated with PD-1 inhibitors from January 2018 to November 2022 at the First Affiliated Hospital of Guangxi Medical University were retrospectively analyzed.

Research results
Our study confirmed that Eastern Cooperative Oncology Group performance status, CAR and tumor number were independent prognostic factors for overall survival, while CAR, tumor number and neutrophil-to-lymphocyte ratio were independent prognostic factors for progression-free survival. Nomogram based on CAR can well evaluate the risk level of patients with liver cancer treated with PD-1 inhibitors.

Research conclusions
In this study, the CAR was found to be a potential predictor of short- and long-term prognosis in patients with HCC treated with PD-1 inhibitors. The CAR-based construct of nomogram achieved individualized prediction for patients.

Research perspectives
Further multi-center, large-sample clinical and randomized controlled studies are still needed to help identify additional risk factors for HCC in patients treated with PD-1 inhibitors.

FOOTNOTES

Co-first authors: Bai-Bei Li and Lei-Jie Chen.

Author contributions: Li BB, Chen LJ and Yu SP designed the study; Lu SL, Lei B and Yu GL collected the data; Li BB, Lu SL and Yu SP assembled the data; Li BB, Chen LJ and Yu SP analysed, interpreted the data and wrote the article; all authors read and approved the final manuscript. Bai-Bei Li and Lei-Jie Chen contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study.

Supported by the Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor (Guangxi Medical University), Ministry of Education, No. GKE-ZZ202117 and No. GKE-ZZ202334.

Institutional review board statement: This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Approval No.2023-E332-01).

Informed consent statement: All participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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S-Editor: Lin C
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Yang JD**, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589-604 [PMID: 31439937 DOI: 10.1038/s41575-019-0186-y]

2 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

3 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin* 2021; **71**: 7-33 [PMID: 33433946 DOI: 10.3322/caac.21654]

4 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

5 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]

6 **Marrero JA**, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018; **68**: 723-750 [PMID: 29624699 DOI: 10.1002/hep.29913]

7 **Bouattour M**, Mehta N, He AR, Cohen EI, Nault JC. Systemic Treatment for Advanced Hepatocellular Carcinoma. *Liver Cancer* 2019; **8**: 341-358 [PMID: 31768344 DOI: 10.1159/000496439]

8 **Brown ZJ**, Greten TF, Heinrich B. Adjuvant Treatment of Hepatocellular Carcinoma: Prospect of Immunotherapy. *Hepatology* 2019; **70**: 1437-1442 [PMID: 30927283 DOI: 10.1002/hep.30633]

9 **Rimassa L**, Pressiani T, Merle P. Systemic Treatment Options in Hepatocellular Carcinoma. *Liver Cancer* 2019; **8**: 427-446 [PMID: 31799201 DOI: 10.1159/000499765]

10 **Gou H**, Liu S, Liu L, Luo M, Qin S, He K, Yang X. Obeticholic acid and 5β-cholanic acid 3 exhibit anti-tumor effects on liver cancer through CXCL16/CXCR6 pathway. *Front Immunol* 2022; **13**: 1095915 [PMID: 36605219 DOI: 10.3389/fimmu.2022.1095915]

11 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]

12 **Macek Jilkova Z**, Aspord C, Decaens T. Predictive Factors for Response to PD-1/PD-L1 Checkpoint Inhibition in the Field of Hepatocellular Carcinoma: Current Status and Challenges. *Cancers (Basel)* 2019; **11** [PMID: 31615069 DOI: 10.3390/cancers11101554]

13 **Markham A**, Keam SJ. Camrelizumab: First Global Approval. *Drugs* 2019; **79**: 1355-1361 [PMID: 31313098 DOI: 10.1007/s40265-019-01167-0]

14 **Zhu AX**, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]

15 **Finn RS**, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, Breder V, Edeline J, Chao Y, Ogasawara S, Yau T, Garrido M, Chan SL, Knox J, Daniele B, Ebbinghaus SW, Chen E, Siegel AB, Zhu AX, Cheng AL; KEYNOTE-240 investigators. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol* 2020; **38**: 193-202 [PMID: 31790344 DOI: 10.1200/JCO.19.01307]

16 **Chan TA**, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, Peters S. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol* 2019; **30**: 44-56 [PMID: 30395155 DOI: 10.1093/annonc/mdy495]

17 **Ribas A**, Hu-Lieskovan S. What does PD-L1 positive or negative mean? *J Exp Med* 2016; **213**: 2835-2840 [PMID: 27903604 DOI: 10.1084/jem.20161462]

18 **Patel SP**, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. *Mol Cancer Ther* 2015; **14**: 847-856 [PMID: 25695955 DOI: 10.1158/1535-7163.MCT-14-0983]

19 **Schulze K**, Imbeaud S, Letouzé E, Alexandrov LB, Calderaro J, Rebouissou S, Couchy G, Meiller C, Shinde J, Soysouvanh F, Calatayud AL, Pinyol R, Pelletier L, Balabaud C, Laurent A, Blanc JF, Mazzaferro V, Calvo F, Villanueva A, Nault JC, Bioulac-Sage P, Stratton MR, Llovet JM, Zucman-Rossi J. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat Genet* 2015; **47**: 505-511 [PMID: 25822088 DOI: 10.1038/ng.3252]

20 **Samstein RM**, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, Hakimi AA, Voss MH, Russo P, Rosenberg J, Iyer G, Bochner BH, Bajorin DF, Al-Ahmadie HA, Chaft JE, Rudin CM, Riely GJ, Baxi S, Ho AL, Wong RJ, Pfister DG, Wolchok JD, Barker CA, Gutin PH, Brennan CW, Tabar V, Mellinghoff IK, DeAngelis LM, Ariyan CE, Lee N, Tap WD, Gounder MM, D'Angelo SP, Saltz L, Stadler ZK, Scher HI, Baselga J, Razavi P, Klebanoff CA, Yaeger R, Segal NH, Ku GY, DeMatteo RP, Ladanyi M, Rizvi NA, Berger MF, Riaz N, Solit DB, Chan TA, Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet* 2019; **51**: 202-206 [PMID: 30643254 DOI: 10.1038/s41588-018-0312-8]

21 **Herbst RS**, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G Jr, Garrido M, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; **387**: 1540-1550 [PMID: 26712084 DOI: 10.1016/S0140-6736(15)01281-7]

22 **Sangro B**, Melero I, Wadhawan S, Finn RS, Abou-Alfa GK, Cheng AL, Yau T, Furuse J, Park JW, Boyd Z, Tang HT, Shen Y, Tschaika M, Neely J, El-Khoueiry A. Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma. *J Hepatol* 2020; **73**: 1460-1469 [PMID: 32710922 DOI: 10.1016/j.jhep.2020.07.026]

23 **Calderaro J**, Rousseau B, Amaddeo G, Mercey M, Charpy C, Costentin C, Luciani A, Zafrani ES, Laurent A, Azoulay D, Lafdil F, Pawlotsky JM. Programmed death ligand 1 expression in hepatocellular carcinoma: Relationship With clinical and pathological features. *Hepatology* 2016; **64**: 2038-2046 [PMID: 27359084 DOI: 10.1002/hep.28710]

24 **Sia D**, Jiao Y, Martinez-Quetglas I, Kuchuk O, Villacorta-Martin C, Castro de Moura M, Putra J, Camprecios G, Bassaganyas L, Akers N, Losic B, Waxman S, Thung SN, Mazzaferro V, Esteller M, Friedman SL, Schwartz M, Villanueva A, Llovet JM. Identification of an Immune-specific Class of Hepatocellular Carcinoma, Based on Molecular Features. *Gastroenterology* 2017; **153**: 812-826 [PMID: 28624577 DOI: 10.1053/j.gastro.2017.06.007]

25 **Mehnert JM**, Monjazeb AM, Beerthuijzen JMT, Collyar D, Rubinstein L, Harris LN. The Challenge for Development of Valuable Immuno-oncology Biomarkers. *Clin Cancer Res* 2017; **23**: 4970-4979 [PMID: 28864725 DOI: 10.1158/1078-0432.CCR-16-3063]

26 **Kim HD**, Park S, Jeong S, Lee YJ, Lee H, Kim CG, Kim KH, Hong SM, Lee JY, Kim S, Kim HK, Min BS, Chang JH, Ju YS, Shin EC, Song

GW, Hwang S, Park SH. 4-1BB Delineates Distinct Activation Status of Exhausted Tumor-Infiltrating CD8(+) T Cells in Hepatocellular Carcinoma. *Hepatology* 2020; **71**: 955-971 [PMID: 31353502 DOI: 10.1002/hep.30881]

27 **Keenan BP**, Fong L, Kelley RK. Immunotherapy in hepatocellular carcinoma: the complex interface between inflammation, fibrosis, and the immune response. *J Immunother Cancer* 2019; **7**: 267 [PMID: 31627733 DOI: 10.1186/s40425-019-0749-z]

28 **Xu Y**, Yuan X, Zhang X, Hu W, Wang Z, Yao L, Zong L. Prognostic value of inflammatory and nutritional markers for hepatocellular carcinoma. *Medicine (Baltimore)* 2021; **100**: e26506 [PMID: 34160470 DOI: 10.1097/MD.0000000000026506]

29 **Diakos CI**, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014; **15**: e493-e503 [PMID: 25281468 DOI: 10.1016/S1470-2045(14)70263-3]

30 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959 DOI: 10.1038/nature01322]

31 **Li B**, Deng H, Zhou Z, Tang B. The Prognostic value of the Fibrinogen to pre-albumin ratio in malignant tumors of the digestive system: a systematic review and meta-analysis. *Cancer Cell Int* 2022; **22**: 22 [PMID: 35033080 DOI: 10.1186/s12935-022-02445-w]

32 **Li B**, Deng H, Lei B, Chen L, Zhang X, Sha D. The prognostic value of fibrinogen to albumin ratio in malignant tumor patients: A meta-analysis. *Front Oncol* 2022; **12**: 985377 [PMID: 36249067 DOI: 10.3389/fonc.2022.985377]

33 **Liu Y**, Zhao S, Du W, Tian Z, Chi H, Chao C, Shen W. Applying interpretable machine learning algorithms to predict risk factors for permanent stoma in patients after TME. *Front Surg* 2023; **10**: 1125875 [PMID: 37035560 DOI: 10.3389/fsurg.2023.1125875]

34 **Gong Z**, Xin R, Li L, Lv L, Wu X. Platelet-to-lymphocyte ratio associated with the clinicopathological features and prognostic value of breast cancer: A meta-analysis. *Int J Biol Markers* 2022; **37**: 339-348 [PMID: 35971299 DOI: 10.1177/03936155221118098]

35 **Huang Y**, Chen Y, Zhu Y, Wu Q, Yao C, Xia H, Li C. Postoperative Systemic Immune-Inflammation Index (SII): A Superior Prognostic Factor of Endometrial Cancer. *Front Surg* 2021; **8**: 704235 [PMID: 34746222 DOI: 10.3389/fsurg.2021.704235]

36 **Petrucci GN**, Lobo L, Queiroga F, Martins J, Prada J, Pires I, Henriques J. Neutrophil-to-lymphocyte ratio is an independent prognostic marker for feline mammary carcinomas. *Vet Comp Oncol* 2021; **19**: 482-491 [PMID: 33576562 DOI: 10.1111/vco.12686]

37 **Kubota K**, Ito R, Narita N, Tanaka Y, Furudate K, Akiyama N, Chih CH, Komatsu S, Kobayashi W. Utility of prognostic nutritional index and systemic immune-inflammation index in oral cancer treatment. *BMC Cancer* 2022; **22**: 368 [PMID: 35392843 DOI: 10.1186/s12885-022-09439-x]

38 **Tokuyama N**, Takegawa N, Nishikawa M, Sakai A, Mimura T, Kushida S, Tsumura H, Yamamoto Y, Miki I, Tsuda M. Pretreatment Glasgow prognostic score as a predictor of outcomes in nivolumab-treated patients with advanced gastric cancer. *PLoS One* 2021; **16**: e0247645 [PMID: 33635904 DOI: 10.1371/journal.pone.0247645]

39 **Ren Y**, Fan X, Chen G, Zhou D, Lin H, Cai X. Preoperative C-reactive protein/albumin ratio to predict mortality and recurrence of patients with hepatocellular carcinoma after curative resection. *Med Clin (Barc)* 2019; **153**: 183-190 [PMID: 30606506 DOI: 10.1016/j.medcli.2018.11.010]

40 **Huang ZZ**, Wen W, Hua X, Song CG, Bi XW, Huang JJ, Xia W, Yuan ZY. Establishment and Validation of Nomogram Based on Combination of Pretreatment C-Reactive Protein/Albumin Ratio-EBV DNA Grade in Nasopharyngeal Carcinoma Patients Who Received Concurrent Chemoradiotherapy. *Front Oncol* 2021; **11**: 583283 [PMID: 34336633 DOI: 10.3389/fonc.2021.583283]

41 **Xie Q**, Wang L, Zheng S. Prognostic and Clinicopathological Significance of C-Reactive Protein to Albumin Ratio in Patients With Pancreatic Cancer: A Meta-Analysis. *Dose Response* 2020; **18**: 1559325820931290 [PMID: 32647499 DOI: 10.1177/1559325820931290]

42 **Bao Y**, Yang J, Duan Y, Chen Y, Chen W, Sun D. The C-reactive protein to albumin ratio is an excellent prognostic predictor for gallbladder cancer. *Biosci Trends* 2021; **14**: 428-435 [PMID: 33239498 DOI: 10.5582/bst.2020.03326]

43 **Dai M**, Wu W. Prognostic role of C-reactive protein to albumin ratio in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Front Oncol* 2023; **13**: 1148786 [PMID: 37213304 DOI: 10.3389/fonc.2023.1148786]

44 **Pathak A**, Agrawal A. Evolution of C-Reactive Protein. *Front Immunol* 2019; **10**: 943 [PMID: 31114584 DOI: 10.3389/fimmu.2019.00943]

45 **Dutta S**, Fullarton GM, Forshaw MJ, Horgan PG, McMillan DC. Persistent elevation of C-reactive protein following esophagogastric cancer resection as a predictor of postoperative surgical site infectious complications. *World J Surg* 2011; **35**: 1017-1025 [PMID: 21350898 DOI: 10.1007/s00268-011-1002-1]

46 **Sproston NR**, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front Immunol* 2018; **9**: 754 [PMID: 29706967 DOI: 10.3389/fimmu.2018.00754]

47 **Lai CC**, You JF, Yeh CY, Chen JS, Tang R, Wang JY, Chin CC. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. *Int J Colorectal Dis* 2011; **26**: 473-481 [PMID: 21190025 DOI: 10.1007/s00384-010-1113-4]

48 **Fuhrman MP**. The albumin-nutrition connection: separating myth from fact. *Nutrition* 2002; **18**: 199-200 [PMID: 11844655 DOI: 10.1016/s0899-9007(01)00729-8]

49 **Gupta D**, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J* 2010; **9**: 69 [PMID: 21176210 DOI: 10.1186/1475-2891-9-69]

50 **Otranto M**, Souza-Netto I, Aguila MB, Monte-Alto-Costa A. Male and female rats with severe protein restriction present delayed wound healing. *Appl Physiol Nutr Metab* 2009; **34**: 1023-1031 [PMID: 20029510 DOI: 10.1139/H09-100]

51 **Fanali G**, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. *Mol Aspects Med* 2012; **33**: 209-290 [PMID: 22230555 DOI: 10.1016/j.mam.2011.12.002]

52 **Wojtowicz ME**, Dunn BK, Umar A. Immunologic approaches to cancer prevention-current status, challenges, and future perspectives. *Semin Oncol* 2016; **43**: 161-172 [PMID: 26970135 DOI: 10.1053/j.seminoncol.2015.11.001]

53 **Fu X**, Yang Y, Zhang D. Molecular mechanism of albumin in suppressing invasion and metastasis of hepatocellular carcinoma. *Liver Int* 2022; **42**: 696-709 [PMID: 34854209 DOI: 10.1111/liv.15115]

54 **Zhang F**, Lu SX, Hu KS, Gan YH, Chen Y, Ge NL, Yang BW, Zhang L, Chen RX, Ren ZG, Yin X. Albumin-to-alkaline phosphatase ratio as a predictor of tumor recurrence and prognosis in patients with early-stage hepatocellular carcinoma undergoing radiofrequency ablation as initial therapy. *Int J Hyperthermia* 2021; **38**: 1-10 [PMID: 33400889 DOI: 10.1080/02656736.2020.1850885]

55 **Mai RY**, Bai T, Luo XL, Wu GB. Preoperative fibrinogen-to-albumin ratio predicts the prognosis of patients with hepatocellular carcinoma subjected to hepatectomy. *BMC Gastroenterol* 2022; **22**: 261 [PMID: 35606690 DOI: 10.1186/s12876-022-02328-4]

56 **Katayama K**, Imai T, Abe Y, Nawa T, Maeda N, Nakanishi K, Wada H, Fukui K, Ito Y, Yokota I, Ohkawa K. Number of Nodules but not Size of Hepatocellular Carcinoma Can Predict Refractoriness to Transarterial Chemoembolization and Poor Prognosis. *J Clin Med Res* 2018; **10**: 765-771 [PMID: 30214648 DOI: 10.14740/jocmr3559w]

57 **Yao J**, Zhu X, Wu Z, Wei Q, Cai Y, Zheng Y, Hu X, Hu H, Zhang X, Pan H, Zhong X, Han W. Efficacy and safety of PD-1 inhibitor

combined with antiangiogenic therapy for unresectable hepatocellular carcinoma: A multicenter retrospective study. *Cancer Med* 2022; **11**: 3612-3622 [PMID: 35403359 DOI: 10.1002/cam4.4747]

58 **Mouchli M**, Reddy S, Gerrard M; Boardman L, Rubio M. Usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic predictor after treatment of hepatocellular carcinoma." Review article. *Ann Hepatol* 2021; **22**: 100249 [PMID: 32896610 DOI: 10.1016/j.aohep.2020.08.067]

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