Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Prognostic Value of Peripheral Blood Inflammatory Markers in Hepatocellular Carcinoma Treated with Lenvatinib Combined with PD-1 Inhibitors

Yujing Xin[1], Ning Liu[2], Gang Peng[3], Xiaoyu Huang[3], Xiaojing Cao[3], Xiang Zhou[3]

[1]Department of Oncology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China; [2]School of Software, Shandong University, Jinan, Shandong, 250101, People's Republic of China; [3]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China

Correspondence: Xiang Zhou, Email zhou.xiang@yeah.net

Purpose: To investigate the prognostic value of inflammatory indexes based on peripheral blood cells in unresectable hepatocellular carcinoma (HCC) patients treated with Lenvatinib combined with PD-1 inhibitors.

Methods: This study retrospectively collected baseline inflammatory indexes from HCC patients received Lenvatinib and PD-1 inhibitor-based combination therapy at the Cancer Hospital of the Chinese Academy of Medical Sciences between October 2018 and October 2021. The optimal threshold values for inflammatory indexes determined using X-tile. The factors related to treatment response and survival outcomes were analyzed through logistic regression and Cox regression, respectively. A novel preoperative prognostic nomogram was constructed based on inflammatory indexes, and the predictive efficacy of the nomogram and BCLC staging was compared by the area under the ROC curve.

Results: 156 eligible patients with unresectable HCC were included, with median OS and PFS of 23.8 and 11.5 months, respectively, and ORR of 48.7%. The baseline SIRI was an independent factor of treatment response, with a significantly higher ORR for patients with a SIRI <0.8 than for patients with a SIRI ≥0.8 (59.7% vs 41.5%, P=0.03). SIRI and PNI were independent prognostic factors of PFS, and SIRI was an independent prognostic factor of OS. The AUC value of nomogram based on baseline SIRI, PNI, and tumor distribution in predicting the 6-,12- and 18-month PFS of patients was significantly higher than that of traditional BCLC stage, and its prediction performance was substantially better than that of BCLC stage system (C-index, 0.730 vs 0.535).

Conclusion: The baseline SIRI could be used as a potential non-invasive biomarker to predict the efficacy and survival benefit of immune combination therapy for HCC. The nomogram based on inflammation indexes could achieve better prediction performance and help clinicians to identify high-risk patients and formulate treatment plans.

Keywords: lenvatinib, PD-1 inhibitor, inflammatory indexes, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) stands as the predominant form of primary liver cancer and is recognized globally as a major contributor to cancer-related fatalities.[1] The incidence rate of primary HCC in China accounts for more than half of the global total.[2,3] Individuals diagnosed with early-stage HCC have the potential to attain an optimistic prognosis through the application of curative interventions, which encompass procedures such as surgical liver resection, liver transplantation, or local ablation therapies. However, most HCC patients are diagnosed as unresectable intermediate and advanced-stage HCC, and these patients struggle to achieve long-term survival due to significant tumor heterogeneity.[4]

The continuous updating of systemic therapies such as immune checkpoint inhibitors (ICIs) and molecular targeting agents (MTAs) and has changed the therapeutic prospects of unresectable HCC.[5,6] The first-line MTA such as sorafenib

Received: 27 August 2024
Accepted: 15 November 2024
Published: 24 January 2025

or Lenvatinib may moderately prolong survival in patients with unresectable HCC.[7] Previous clinical trials have shown pembrolizumab or nivolumab to exhibit promising anti-tumor efficacy in HCC.[8,9] Unfortunately, the survival prognosis of patients with HCC remains poor due to low response to MTA or ICI monotherapy. Surprisingly, the combination therapy of MTA and ICIs, such as Atezolizumab plus bevacizumab,[10] bevacizumab biosimilar plus sintilimab,[11] lenvatinib plus pembrolizumab,[12] apatinib plus camrelizumab,[13] have broken through the current bottleneck in the treatment strategy of unresectable HCC with excellent anti-tumor efficacy. However, patients respond differently to immunotherapy due to the heterogeneity and complex etiology of HCC.

Exploration of biomarkers of immunotherapy has been a research hotspot in cancer immunotherapy. Current biomarker studies on immunotherapy of HCC mainly included tumor genomic features, tumor mutation burden, PD-L1 expression, and microsatellite instability.[14,15] However the clinical application of these biomarkers was limited due to invasive operations and high costs. An increasing number of researches indicated that the immunological nutritional status and inflammatory status are closely related to the prognosis of cancer patients.[16–18] Inflammation-based scores, such as the Neutrophil lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR), Lymphocyte monocyte ratio (LMR), Prognostic nutrition index (PNI), Systemic immune-inflammatory index (SII), Systemic inflammatory response index (SIRI) and the C-reactive protein (CRP), have shown good prognostic value in immunotherapy for esophageal cancer, non-small cell lung cancer, and intrahepatic cholangiocarcinoma.[19–22] Various inflammatory scores such as PLR, NLR, SII, and PNI have been shown to serve as predictors to predict the survival of surgical or local treatment for HCC.[23–26] Importantly, NLR $\geq$ 5 and PLR $\geq$ 300 have been reported to serve as biomarkers in unresectable HCC patients treated with Atezolizumab plus Bevacizumab.[27] A previous study reported that patients with an NLR<5 both pre- and post-nivolumab had significantly improved OS compared to patients with an NLR $\geq$ 5 pre- and posttreatment. There was also a significant inverse relationship between OS and PLR tertiles (<119; $\geq$ 119 and <224; $\geq$ 224).[28] In addition, survival outcomes of HCC patients treated with anti-PD -1 therapy with PNI >48 were reported to be superior to those with PNI $\leq$ 48.[29]

Up to now, the prognostic value of inflammatory indicators derived from peripheral blood in HCC immunotherapy has not been fully elucidated. Accordingly, the main objective of this study was to explore the predictive value of peripheral blood inflammatory markers in HCC patients receiving the combination therapy of TKIs and ICIs. Subsequently, this study would establish a novel and efficient predictive model to assist clinicians in selecting patients who benefit from combination therapy and guiding individualized treatment plans.

Materials and Methods

Study Population

The patients diagnosed with unresectable HCC from the National Cancer Center were included in this study between October 2018 and December 2021. The inclusion criteria for this study were as follows: unresectable HCC diagnosed as Barcelona Clinic Liver Cancer (BCLC) B or C stage by clinical guidelines,[4,30] 18–75 years old years old, Eastern Cooperative Oncology Group Performance Status score (ECOG PS) of 0–1, liver function as Child-Pugh A or B class ($\leq$ 7 points), Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)<3 times the upper limit of normal values, Total bilirubin (TBIL)<1.5 times the upper limit of normal value, HBV DNA$\leq$ 500 IU/mL, at least one measurable target lesion evaluated based on modified Response Evaluation Criteria in Solid Tumors (mRECIST),[31] and appropriate hematologic and organ function. The exclusion criteria were as follows: $\geq$75 years old years old, active autoimmune disease, the patient had previously received antitumor treatment, such as TKIs, ICIs, and local interventional therapy, other malignant tumors, incomplete medical information, symptomatic brain metastasis, and loss of follow-up.

This study was approved by the Institutional Review Boards of the National Cancer Center (NCC2019KZ-010) and complied with the ethical guidelines of the 1975 Declaration of Helsinki, Written informed consent for the treatment was obtained from each patient. The need for written informed consent to publish the data was waived by the Ethics Committees, since the personal details of these patients were kept confidential.

Treatment Procedure

Eligible patients who received the combination therapy participated in this study. The treatment plan was ultimately decided by the multidisciplinary consultation team. Patients were given either 8mg or 12mg of Lenvatinib orally daily and a PD-1 inhibitor, including camrelizumab (Hengrui Pharma, Lianyungang, China), tislelizumab (BeiGene, Shanghai, China) and sintilimab (Innovent Biologics, Suzhou, China). Treatment interruption or dose adjustment may be due to the disease progression and intolerable drug toxicity.

Data Collection and Follow-Up

Neutrophil, lymphocyte, monocyte, and platelet counts from peripheral blood ≤1 week before combination therapy and other required clinical parameters were also collected. Variables included maximum tumor diameter, tumor number, hepatitis B virus (HBV) infection, presence of liver cirrhosis, Child-Pugh grade, ALBI grade, serum alpha-fetoprotein (AFP), aspartate transaminotransferase (AST), total bilirubin (TBIL), alanine aminotransferase (ALT), serum glutamyl-transferase (GGT) level, albumin (ALB), C-reactive protein. The calculation formulas of inflammatory scores based on peripheral blood cells were as follows:

(1) PNI = 10 albumin (g/dL) + 0.005 total lymphocyte number (/ μ L).
(2) NLR = neutrophil count/lymphocyte count.
(3) SII= platelet count, neutrophil count/lymphocyte count.
(4) PLR = platelet count/lymphocyte count.
(5) LMR = lymphocyte count/monocyte count.
(6) SIRI = neutrophil count × monocyte count/lymphocyte count.
(7) APRI = aspartate aminotransferase/platelet count.
(8) ANRI = aspartate aminotransferase/neutrophil count.

A comprehensive evaluation of treatment response based on imaging and clinical indicators would be conducted every two treatment cycles until the patient's disease progresses or death and the final follow-up period will be until February 28, 2023.

Outcomes and Assessments

The primary endpoints were overall survival (OS) and progression-free survival (PFS). OS was the time interval from initial therapy to death from any cause and PFS was the time from initial treatment to first progression or death. Treatment response as assessed by mRECIST was the secondary endpoints. Tumor response was assessed by contrast-enhanced MR or CT every 4 to 8 weeks and classified as progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR) based on mRECIST. The "treatment response" in this study referred to the optimal tumor response among all tumor evaluation time points. The patients were divided into two groups according to the optimal tumor response, of which the patients with CR and PR were the treatment responder group (R group), and the patients with SD and PD were the treatment non-responder group (NR group). The best objective response rate (ORR)= (CR + PR) / 100% of total patients, and the disease control rate (DCR)= (CR + PR + SD) / 100% of total patients.

Statistical Analysis

Baseline characteristics and response rates were expressed in terms of frequencies and percentages, and variables were indicated as either the mean (range) or median (standard deviation). Categorical and continuous variables were analyzed with chi-square and t-tests, respectively. The Kaplan–Meier method was used to estimate OS and PFS, and univariate and multivariate regression analyses were used to analyze the prognostic factors of OS and PFS. The survival prediction model (6,12 and 18 months PFS) was calculated by multiple factor analysis (variables with P values<0.05), and internal validation was achieved through five hundred bootstraps resamples. The performance of the prediction model was evaluated by the concordance index (C-index) and time-dependent receiver operating characteristic (t-ROC) curve. The optimal cut-off value for the inflammatory scores was evaluated by the X-tile 3.6.1 software.[32] Data analysis and graphical visualization were implemented using R software (version 3.6.2). $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Patients

Table 1 shows the baseline characteristics of the patients who participated in the study. A total of 156 eligible HCC patients participated in this study, with a mean age of 55.7 years, 131 male patients (84.0%), and 140 hBV-infected patients (89.7%). The overall tumor burden of the patients was high, and the mean diameter of the largest tumor was 10.0cm (median 9.0cm, range 1.2~26.1cm). There were 96 patients with BCLC stage C (61.5%), 62 patients with portal vein tumor thrombus (39.7%), and 56 patients with extrahepatic metastases (35.9%).

Table 1 Patient Demographics and Clinical Characteristics

Characteristics	Total (n=156)	R Group (n=76)	NR Group (n=80)	P value
Sex				0.108
Male	131	68	63	
Female	25	8	17	
Age, median(range) years				1
<60	116	57	59	
≥60	40	19	21	
ECOG-PS				0.236
0	150	75	75	
1	6	1	5	
Hepatitis B				0.914
Yes	140	69	71	
No	16	7	9	
Cirrhosis				0.418
Yes	80	42	38	
No	76	34	42	
Child-Pugh grade				0.714
A	138	66	72	
B	18	10	8	
Largest-tumor size (mean, cm)				0.135
<10	88	48	40	
≥10	68	28	40	
Tumor number				0.364
Single	109	26	21	
Multiple	47	50	59	
Tumor distribution				0.05
Single lobe	85	48	37	
Double lobe	71	28	43	
PVTT				1
Yes	94	46	48	
No	62	30	32	
Extrahepatic metastasis				0.942
Yes	56	48	52	
No	100	28	28	
BCLC stage				0.569
B	60	27	33	
C	96	49	47	
AFP (ng/mL)				0.892
<400	84	40	44	
≥400	72	36	36	

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n=156)	R Group (n=76)	NR Group (n=80)	P value
AST (U/L)				0.786
<40	102	25	29	
≥40	54	51	51	
ALT ((U/L)				0.764
<40	83	39	44	
≥40	73	37	36	
ALB (g/l)				1
<40	108	53	55	
≥40	48	23	25	
TBIL (μmol/l)				0.739
<17.1	81	41	40	
≥17.1	75	35	40	
PLT (10^9/L)				0.694
<100	12	7	5	
≥100	144	69	75	
GGT (U/L)				0.233
<50	28	17	11	
≥50	128	59	69	

Note: Data were presented as n (%) or mean ± standard deviation.
Abbreviations: R, treatment responder; NR, treatment non-responder; ECOG-PS, Eastern Cooperative Oncology Group performance status; PVTT, portal vein tumor thrombus; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; PLT, platelet; GGT, g-glutamyl transpeptidase.

In this study, all patients received at least two cycles of combination therapy with a total of 1233 cycles of PD-1 inhibitor (median 7 cycles) and a median duration of Lenvatinib of 10.8 months.

The Optimal Cut-off (Threshold) for Inflammatory Scores

To avoid different standard deviations in the threshold values of inflammatory scores in this cohort, the optimal cut-off values for PLR, LMR, NLR, SII, SIRI, APRI, PNI, ANRI, and CRP associated with PFS were determined in this study by uniformly using the X-tile. The optimal cut-off values for PLR, LMR, NLR, SII, SIRI, APRI, PNI, ANRI, and CRP were 78.1, 5.3, 4.4, 244.8, 0.8, 53.0, 0.6, 10.4, and 0.3, respectively.

The Correlation Between Inflammatory Indicators and Treatment Response

The ORR in this study was 48.7% and the DCR was 75.0% based on the mRECIST criteria. Patients were divided into treatment responder group and non-responder group based on treatment response, with patients with CR and PR as the treatment responder group (76 patients, 48.7%) and patients with SD and PD as the treatment non-responder group (80 patients, 51.3%). The median PFS and OS of patients in the treatment responder group were 19.8 months and 30.9 months, respectively, which were significantly higher than those of patients in the treatment non-responder group, which were 9.5 months and 18.4 months (Figure 1: Kaplan-Meier curves for PFS (A) and OS (B) of patients in the treatment responder (R) and non-responder (NR) group, $P < 0.001$).

In the present study, the further correlation analyses of treatment response (Table 2) showed that the SIRI (<0.8 vs ≥0.8, HR=0.255, P<0.001), was independently associated with treatment response. The ORR of the patients with SIRI <0.8 was significantly higher than that of the patients with SIRI ≥0.8 (59.7% vs 41.5%, P =0.03), which can serve as a potential biomarker for predicting treatment response.

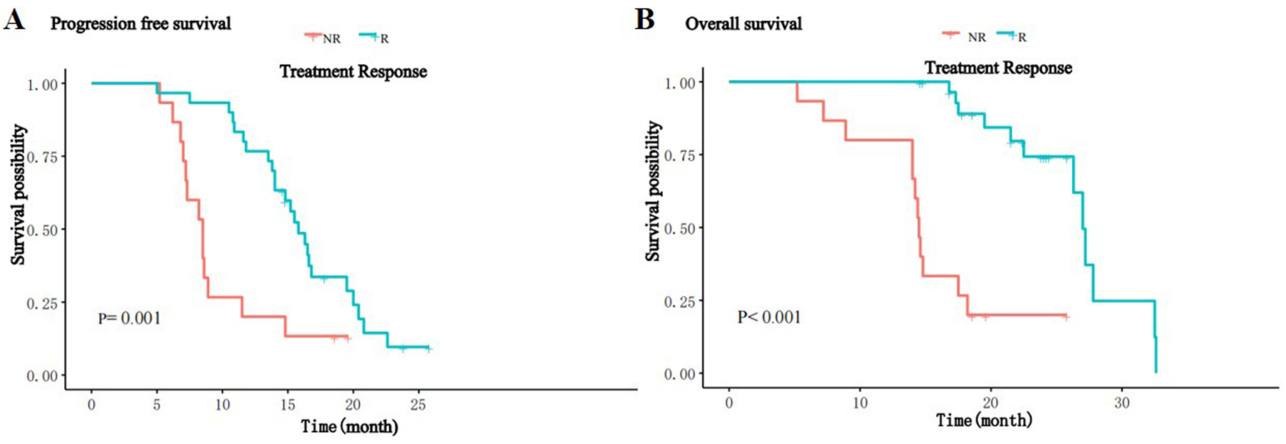

Figure 1 Kaplan-Meier curves for PFS (**A**) and OS (**B**) of patients in the treatment responder (R) and non-responder (NR) group.

The Correlation Between Inflammatory Indicators and Survival

The median follow-up time for participants in the study was 17 months, and by the end of follow-up, median PFS of 11.5 months (95% CI:10.7–13.8 months), and median OS of 23.8 months (95% CI:20.9–29.0 months). The univariate survival analysis indicated that the tumor distribution (double lobe vs single lobe; HR=3.504, P<0.001), CRP (≥0.3 vs <0.3; HR=1.674, P=0.023), SIRI (≥0.8 vs <0.8, HR=1.721, P=0.008) and PNI (<53.0 vs ≥53.0, HR=1.616, P=0.030) were the associated factors of PFS (Table 3). The multifactorial Cox proportional risk regression model showed that SIRI (≥ 0.8 vs<0.8, HR=3.593, P<0.001), PNI (<53.0 vs ≥53.0, HR=1.823, P=0.007), and tumor distribution (double lobe vs single lobe; HR=5.421, P<0.001) were independent influencing factors for PFS (Table 3).

In addition, univariate analysis showed that tumor distribution (double lobe vs single lobe; HR=3.256, P<0.001), portal vein thrombus (yes vs no; HR=1.793, P=0.016), BCLC stage (C vs B; HR=2.606, P<0.001), extrahepatic metastasis (yes vs no; HR=2.272, P<0.001) and SIRI (≥0.8 vs <0.8; HR= 2.027, P=0.006) were relevant factors for

Table 2 Logistic Regression Analysis of Treatment Response

Factor	Logistic Regression			
	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
BCLC stage (C/B)	1.274(0.668–2.445)	0.463		
Largest tumor size (<10/≥10cm)	0.583(0.306–1.102)	0.099		
Tumor distribution (Single lobe/double lobe)	0.275(0.139–0.528)	<0.001	0.170(0.074–0.361)	<0.001
PVTT (Yes/No)	0.978(0.514–1.86)	0.946		
Extrahepatic metastasis (Yes/No)	1.083(0.562–2.089)	0.811		
AFP (<400/≥400ng/mL)	1.100(0.586–2.069)	0.767		
CRP (<0.3/≥0.3mg/L)	0.641(0.318–1.278)	0.209		
NLR (<5.3/≥5.3)	2.538(0.875–8.407)	0.099		
LMR (<4.4/≥4.4)	1.435(0.743–2.79)	0.283		
PLR (<78.1/≥78.1)	0.827(0.295–2.285)	0.712		
SII (<244.8/≥244.8)	0.479(0.157–1.332)	0.169		
SIRI (<0.8/≥0.8)	0.479(0.247–0.915)	0.027	0.255(0.110–0.551)	<0.001
PNI (≥53.0/<53.0)	0.703(0.332–1.464)	0.35		
ANRI (<10.4/≥10.4)	1.333(0.703–2.546)	0.38		
APRI (<0.6/≥0.6)	1.364(0.508–3.77)	0.538		

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; CRP, C-reactive protein.

Table 3 Univariate and Multivariate Analysis of Progression-Free Survival

Factor	Progression-Free Survival			
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P -value*	HR (95% CI)	*P -value*
BCLC stage (C/B)	1.177(0.779–1.778)	0.436	-	-
Largest tumor size (≥10/<10cm)	1.383(0.932–2.053)	0.108	-	-
Tumor distribution (Single lobe/double lobe)	3.504(2.323–5.285)	<0.001	5.421 (3.386–8.677)	<0.001
PVTT (Yes/No)	1.191(0.802–1.769)	0.388	-	-
Extrahepatic metastasis (Yes/No)	1.409(0.947–2.096)	0.095		
AFP (<400/≥400ng/mL)	0.859(0.578–1.276)	0.45	-	-
CRP (≥0.3/<0.3)	1.674(1.056–2.654)	0.023	1.008 (0.604–1.682)	0.977
NLR (≥5.3/<5.3)	0.534(0.247–1.152)	0.08		
LMR (≥4.4/<4.4)	0.764(0.505–1.155)	0.196	-	-
PLR (≥78.1/<78.1)	1.900(0.880–4.100)	0.073		
SII (≥244.8/<244.8)	1.894(0.918–3.909)	0.059		
SIRI (≥0.8/<0.8)	1.721(1.140–2.597)	0.008	3.593 (2.236–5.773)	<0.001
PNI (≥53.0/<53.0)	1.616(1.061–2.461)	0.03	1.823 (1.174–2.830)	0.007
ANRI (≥10.4/<10.4)	0.789(0.531–1.173)	0.244	-	-
APRI (≥0.6/<0.6)	0.571(0.288–1.135)	0.085		

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; CRP, C-reactive protein.

OS (Table 4). The multivariate analysis indicated that SIRI (≥ 0.8 vs<0.8; HR=3.426, P<0.001), tumor distribution (double lobe vs single lobe; HR=4.521, P<0.001), and extrahepatic metastasis (yes vs no; HR=2.235, P=0.019) were independent influencing factors for OS (Table 4).

The Kaplan-Meier curve revealed that the median PFS in patients with SIRI <0.8 and PNI ≥53.0 was significantly longer than the median PFS for patients with SIRI≥ 0.8 and PNI<53.0 (both P-values <0.05, Figure 2: Kaplan-Meier

Table 4 Univariate and Multivariate Analysis of Overall Survival

Factor	Overall Survival			
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P -value*	HR (95% CI)	*P -value*
BCLC stage (C/B)	2.606(1.5–4.526)	<0.001	1.315 (0.504–3.431)	0.575
Largest tumor size (≥10/<10cm)	1.129(0.698–1.823)	0.621		
Tumor distribution (Single lobe/double lobe)	3.256(1.919–5.522)	<0.001	4.521 (2.500–8.178)	<0.001
PVTT (Yes/No)	1.793(1.119–2.875)	0.016	0.841 (0.412–1.714)	0.633
Extrahepatic metastasis (Yes/No)	2.272(1.41–3.661)	<0.001	2.235 (1.139–4.387)	0.019
AFP (<400/≥400)	1.21(0.757–1.935)	0.427		
CRP (≥0.3/<0.3)	1.417(0.808–2.483)	0.21		
NLR (≥5.3/<5.3)	0.894(0.384–2.079)	0.792		
LMR (≥4.4/<4.4)	0.696(0.422–1.147)	0.148		
PLR (≥78.1/<78.1)	1.345(0.539–3.353)	0.508		
SII (≥244.8/<244.8)	1.551(0.623–3.864)	0.315		
SIRI (≥0.8/<0.8)	2.027(1.205–3.411)	0.006	3.426 (1.924–6.099)	<0.001
PNI (≥53.0/<53.0)	1.546(0.924–2.586)	0.106		
ANRI (≥10.4/<10.4)	0.629(0.392–1.01)	0.057		
APRI (≥0.6/<0.6)	0.644(0.277–1.493)	0.276		

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; CRP, C-reactive protein.

https://doi.org/10.2147/JHC.S486910

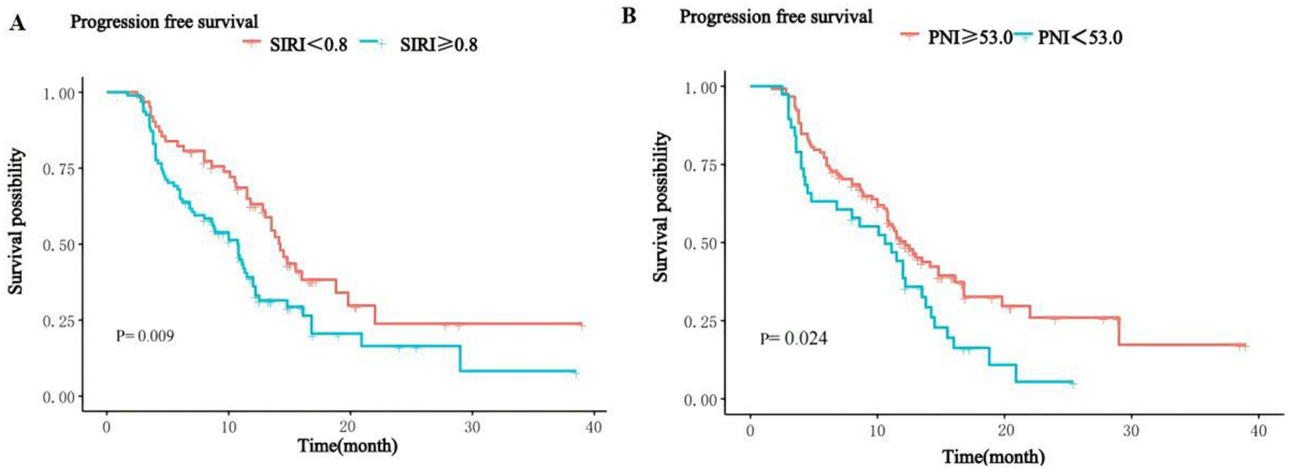

Figure 2 Kaplan-Meier curves for PFS of patients with high and low SIRI (**A**) and PNI (**B**) group.

curves for PFS of patients with high and low SIRI (A) and PNI (B) group). Baseline SIRI was an independent related factor for patient OS, with a median OS of 24.0 months in patients with SIRI <0.8, significantly higher than 19.5 months in patients with SIRI ≥0.8 (P =0.007, Figure 3: Kaplan-Meier curves for OS of patients with high and low SIRI group) and these results suggest that the SIRI was independently associated with patient survival outcome.

Establishment and Verification of the Nomogram

Tumor distribution, SIRI, and PNI constituted a highly efficient nomogram that can predict the 6-,12- and 18-month PFS (Figure 4: Kaplan-Meier curves for OS of patients with high and low SIRI group). The C-index of the present nomogram was superior to the BCLC staging system (0.752 vs 0.535, P < 0.001). The t-AUCs of the nomogram of 6-,12- and 18-month PFS were larger than those of the BCLC staging system (Figure 5A-C: Time-dependent ROC curves of the nomogram and BCLC staging system of 6-(A),12-(B) and 18-(C) month PFS, respectively). The calibration curves for predicting 6-,12- and 18-month PFS were shown in Figure 5D (Calibration curves for predicting 6-, 12- and 18-month PFS).

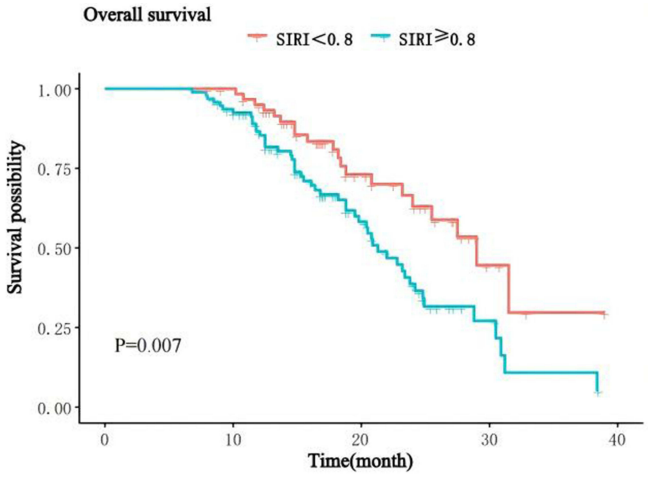

Figure 3 Kaplan-Meier curves for OS of patients with high and low SIRI group.

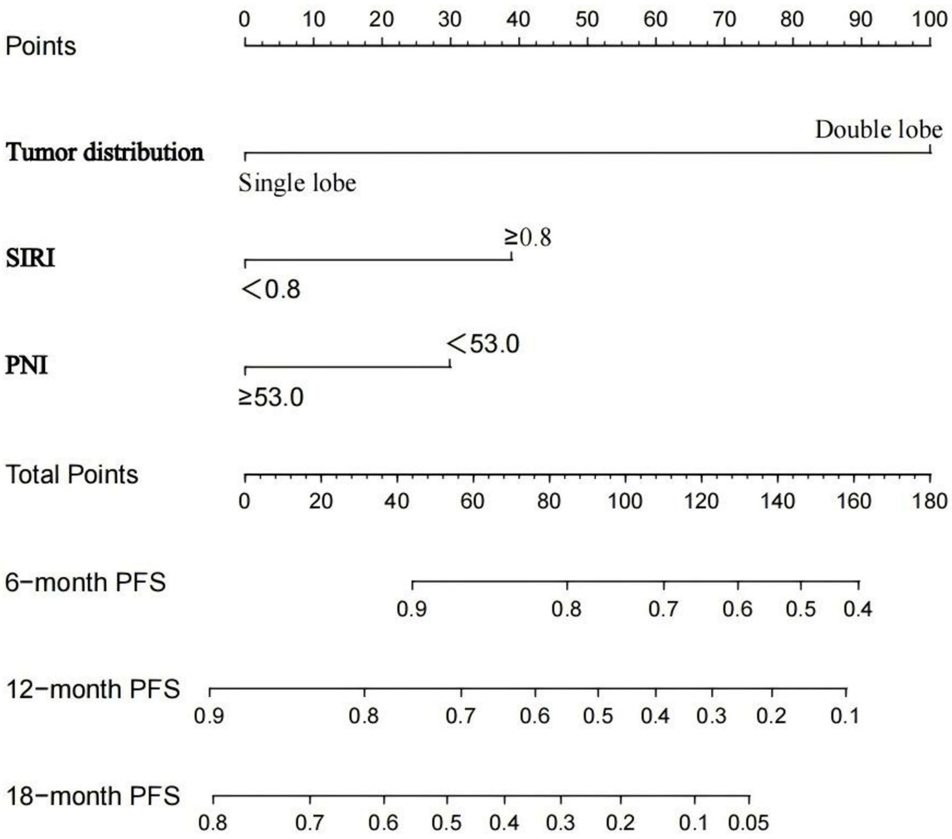

Figure 4 Nomogram for predicting 6-, 12- and 18-month PFS.

Discussion

Increasing evidence suggests that host immune response and systemic inflammation are closely related in cancer patients, and peripheral blood-based inflammatory markers have demonstrated good predictive ability in cancer immunotherapy, with the advantages of objectivity, ease of detection, low cost, and reproducibility[18.] This study explored the impact of baseline inflammatory scores on treatment response and survival prognosis in 156 patients with unresectable HCC treated with a combination of TKI and PD-1 inhibitors. The results of the study showed that baseline SIRI was an independent predictor of therapeutic response to immune-based combination therapy for HCC, with the ORR of patients with SIRI <0.8 being significantly higher than that of patients with SIRI ≥0.8 (59.7% vs 41.5%, P=0.03). In addition, baseline SIRI and PNI were independent prognostic factors for patient survival. Patients with SIRI <0.8 and PNI≥53.0 had significantly longer median PFS than those with SIRI ≥0.8 and PNI <53.0 (both P-values <0.05), and patients with SIRI <0.8 had significantly higher median OS than those with SIRI ≥0.8 (24.0 vs 19.5, P=0.007), and nomograms including tumor distribution, SIRI and PNI was constructed to predict the 6-,12- and 18-month PFS. Therefore, the nomogram can be used by clinicians to develop individualized treatment strategies for HCC patients.

Inflammation is considered a hallmark feature of cancer occurrence and progression.[16,17] The results of this study indicated that SIRI is independently associated with short-term efficacy and long-term survival in patients with u-HCC treated with TKI in combination with PD-1 inhibitors. Neutrophils promote the proliferation, invasion, and metastasis of tumor cells and help tumor cells escape immune surveillance.[33] In addition, cancer-associated inflammatory cytokines such as tumor necrosis factor and IL-6 increase the neutrophil count.[34] In addition, lymphocytes hinder tumor growth by secreting cytokines and inducing cytotoxic cell death, and the decrease in lymphocyte levels can suppress the patient's immune system and accelerate cancer progression.[35,36] Tumor-induced macrophages derived from peripheral monocytes not only disrupt the immune system of tumor patients, but also cause infiltration, proliferation, and metastasis of tumor cells.[37] The circulating monocyte indirectly represents the concentration of tumor-induced macrophages, which is closely

https://doi.org/10.2147/JHC.S486910

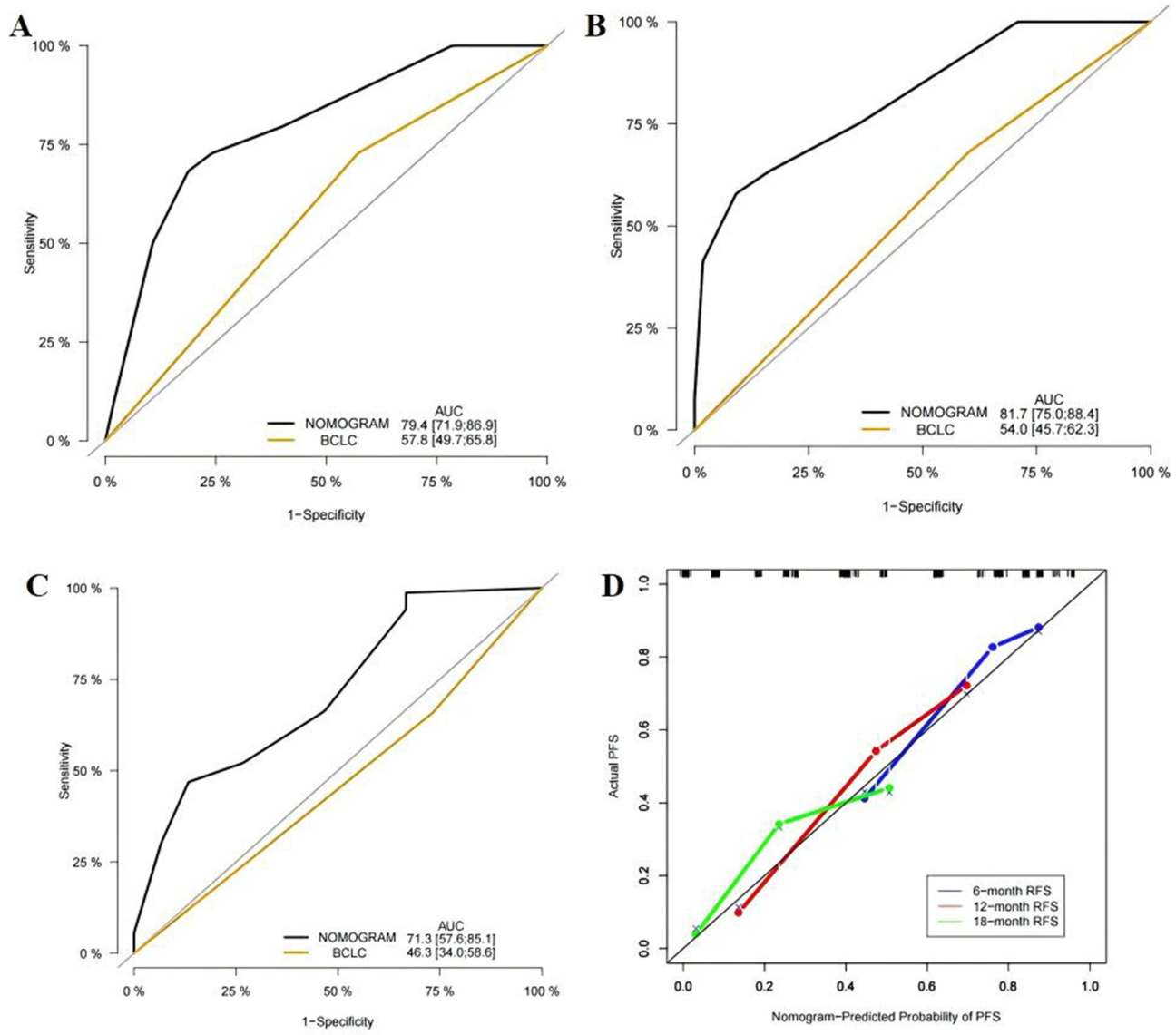

Figure 5 Time-dependent ROC curves of the nomogram and BCLC staging system of 6-(**A**),12-(**B**) and 18-(**C**) month PFS; Calibration curves for predicting 6-, 12- and 18-month PFS(**D**).

related to high tumor burden.[38] Therefore, the tumor-associated inflammation state causes an elevated SIRI and facilitates cancer progression and tumorigenesis, eventually contributing to poor survival prognosis in patients with unresectable HCC.

The nutritional and metabolic status of patients with HCC is closely related to the efficacy and survival benefits of anti-PD-1 therapy.[39] This study found that the baseline nutritional index (PNI) is independently associated with patient PFS and can serve as a non-invasive biomarker for predicting the survival prognosis. PNI derived from albumin and lymphocyte counts in peripheral blood represents the nutritional status of the patient. On the one hand, the key to immunosuppression is the reduction of lymphocyte count (eg, CD8- and CD4-positive T-cells), and lymphopenia leads to reduced immunity.[40] On the other hand, albumin reflects nutritional status and liver function, which may affect the persistence of immunotherapy in HCC patients.[41] Therefore, low levels of PNI may affect the long-term survival of HCC patients by weakening immune system function.[42] In addition, our results suggest that the poor prognosis of patients with double-lobed tumors may be related to the spatial heterogeneity of tumor microenvironment (TME) reported in previous studies.[43–45] And our findings highlight spatial organization as a prominent determinant of tumor progression and provide

valuable insight into the immune evasion mechanisms driving recurrence. In the future we need to validate our studies in larger patient cohorts and focus on mechanisms that may provide a theoretical basis for clinical treatment.

Nomograms are the current simple and efficient model for predicting the recurrence and survival of HCC patients. We established a nomogram based on tumor distribution, SIRI, and PNI to predict PFS in HCC patients and the prediction accuracy of the nomogram was superior to the conventional BCLC staging system. The physician can directly and conveniently predict the PFS by calculating the variable scores in the nomogram. Moreover, this prediction model can help physicians identify high-risk groups and help develop personalized treatment strategies. For high-risk patients, it is recommended to undergo local treatment (such as ablation, TACE, HAIC, radiotherapy, etc.) to reduce tumor burden, and to promptly switch to second-line treatment plans (such as regorafenib, other immune checkpoint inhibitors, etc.) to improve patient survival.

The present study still has some limitations. Firstly, this study was a retrospective single-center study with limited sample size and inherent bias, We will design a multicenter, prospective randomized controlled trial to further validate the conclusions of our study in the future. Secondly, since the heterogeneity of treatment after patients' disease progression may affect the overall survival of patients, we only established a prediction model for PFS instead of OS in this study to ensure the rigor and authenticity of the study. Thirdly, most of the patients participating in this study were HBV-infected HCC, and more patients with other etiologies will be included in the future study.

In conclusion, this study explored the prognostic significance of peripheral blood-based inflammatory scores in unresectable HCC patients treated with the combination therapy of TKIs and ICIs. The preliminary results of this study confirmed that baseline systemic inflammatory response index SIRI was an independent prognostic factor of treatment response and survival outcome. The SIRI is a potential biomarker for the prediction of prognosis in HCC due to its comprehensiveness, simplicity, and low cost in clinical practice. In addition, the comprehensive SIRI-based nomogram presented above may help clinicians to identify high-risk patients and to formulate individualized treatment plans.

Funding

This study was supported by grants from the National Natural Science Foundation of China (62271509), Shandong Provincial Natural Science Foundation (ZR2024QH359), the Joint Funds for the Innovation of Science and Technology, Fujian province (2019KJCX068), and the Mount Taishan Scholar Project Special Fund.

Disclosure

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–132. doi:10.3322/caac.21338
3. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology*. 2019;156(2):477–491.e1. doi:10.1053/j.gastro.2018.08.065
4. Galle PR, Forner A, Llovet JM, et.al, EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019
5. Raoul J-L, Edeline J. Systemic treatment of hepatocellular carcinoma: standard of care in China and elsewhere. *Lancet Oncol*. 2020;21(4):479–481. doi:10.1016/S1470-2045(20)30082-6
6. Zhu X-D, Sun H-C. Emerging agents and regimens for hepatocellular carcinoma. *J Hematol Oncol*. 2019;12(1):110. doi:10.1186/s13045-019-0794-6
7. Faivre S, Rimassa L, Finn RS. Molecular therapies for HCC: looking outside the box. *J Hepatol*. 2020;72(2):342–352. doi:10.1016/j.jhep.2019.09.010
8. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomized, open-label Phase 2 trial. *Lancet Oncol*. 2018;19(7):940–952. doi:10.1016/S1470-2045(18)30351-6
9. Yau T, Park J-W, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, Phase 3 trial. *Lancet Oncol*. 2022;23(1):77–90. doi:10.1016/S1470-2045(21)00604-5
10. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
11. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. *Lancet Oncol*. 2021;22(7):977–990. doi:10.1016/S1470-2045(21)00252-7

12. Finn RS, Ikeda M, Zhu AX, et al. Phase ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. *J Clin Oncol*. 2020;38(26):2960–2970. doi:10.1200/JCO.20.00808
13. Xu J, Shen J, Gu S, et al. Camrelizumab in combination with apatinib in patients with advanced hepatocellular carcinoma (RESCUE): a nonrandomized, open-label, phase II trial. *Clin Cancer Res*. 2021;27(4):1003–1011. doi:10.1158/1078-0432.CCR-20-2571
14. Harding JJ, Nandakumar S, Armenia J, et al. Prospective genotyping of hepatocellular carcinoma: clinical implications of next-generation sequencing for matching patients to targeted and immune therapies. *Clin Cancer Res*. 2019;25(7):2116–2126. doi:10.1158/1078-0432.CCR-18-2293
15. Muhammed A, D'Alessio A, Enica A, et al. Predictive biomarkers of response to immune checkpoint inhibitors in hepatocellular carcinoma. *Expert Rev Mol Diagn*. 2022;22(3):253–264. doi:10.1080/14737159.2022.2049244
16. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–444. doi:10.1038/nature07205
17. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674. doi:10.1016/j.cell.2011.02.013
18. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15(11):e493–e503. doi:10.1016/S1470-2045(14)70263-3
19. Zhang X, Gari A, Li M, et al. Combining serum inflammation indexes at baseline and post treatment could predict pathological efficacy to anti-PD-1 combined with neoadjuvant chemotherapy in esophageal squamous cell carcinoma. *J Transl Med*. 2022;20(1):61. doi:10.1186/s12967-022-03252-7
20. Peng L, Wang Y, Liu F, et al. Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors. *Cancer Immunol Immunother*. 2020;69(9):1813–1822. doi:10.1007/s00262-020-02585-w
21. Bagley SJ, Kothari S, Aggarwal C, et al. Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2017;106:1–7. doi:10.1016/j.lungcan.2017.01.013
22. Yang Z, Zhang D, Zeng H, et al. Inflammation-BASED scores predict responses to PD-1 inhibitor treatment in intrahepatic cholangiocarcinoma. *J Inflamm Res*. 2022;15:5721–5731. doi:10.2147/JIR.S385921
23. Wang D, Bai N, Hu X, et al. Preoperative inflammatory markers of NLR and PLR as indicators of poor prognosis in resectable HCC. *PeerJ*. 2019;7:e7132. doi:10.7717/peerj.7132
24. Zhang D, Huo L, Pan Y, et al. A systemic inflammation response score for prognostic prediction in hepatocellular carcinoma patients after hepatectomy. *J Inflamm Res*. 2022;15:6869–6881. doi:10.2147/JIR.S397375
25. Guo L, Ren H, Pu L, Zhu X, Liu Y, Ma X. The prognostic value of inflammation factors in hepatocellular carcinoma patients with hepatic artery interventional treatments: a retrospective study. *Cancer Manag Res*. 2020;12:7173–7188. doi:10.2147/CMAR.S257934
26. Wang D, Hu X, Xiao L, et al. Prognostic nutritional index and systemic immune-inflammation index predict the prognosis of patients with HCC. *J Gastrointest Surg*. 2021;25(2):421–427. doi:10.1007/s11605-019-04492-7
27. Wu YL, Fulgenzi CAM, D'Alessio A, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as prognostic biomarkers in unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab. *Cancers*. 2022;14(23):5834. doi:10.3390/cancers14235834
28. Dharmapuri S, Özbek U, Lin J-Y, et al. Predictive value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in advanced hepatocellular carcinoma patients treated with anti-PD-1 therapy. *Cancer Med*. 2020;9(14):4962–4970. doi:10.1002/cam4.3135
29. Mei J, Sun X-Q, Lin W-P, et al. Comparison of the prognostic value of inflammation-based scores in patients with hepatocellular carcinoma after anti-PD-1 therapy. *J Inflamm Res*. 2021;14:3879–3890. doi:10.2147/JIR.S325600
30. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358–380. doi:10.1002/hep.29086
31. Llovet JM, Lencioni R. mRECIST for HCC: performance and novel refinements. *J Hepatol*. 2020;72(2):288–306. doi:10.1016/j.jhep.2019.09.026
32. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252–7259. doi:10.1158/1078-0432.CCR-04-0713
33. Yang YM, Kim SY, Seki E. Inflammation and liver cancer: molecular mechanisms and therapeutic targets. *Semin Liver Dis*. 2019;39(1):26–42. doi:10.1055/s-0038-1676806
34. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. *J Intern Med*. 2000;248(3):171–183. doi:10.1046/j.1365-2796.2000.00742.x
35. Gambardella V, Castillo J, Tarazona N, et al. The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target. *Cancer Treat Rev*. 2020;86:102015. doi:10.1016/j.ctrv.2020.102015
36. Chew V, Chen J, Lee D, et al. Chemokine-driven lymphocyte infiltration: an early intratumoural event determining long-term survival in resectable hepatocellular carcinoma. *Gut*. 2012;61(3):427–438. doi:10.1136/gutjnl-2011-300509
37. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell*. 2006;124(2):263–266. doi:10.1016/j.cell.2006.01.007
38. Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol*. 2002;23(11):549–555. doi:10.1016/S1471-4906(02)02302-5
39. Sun K, Chen S, Xu J, Li G, He Y. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2014;140(9):1537–1549. doi:10.1007/s00432-014-1714-3
40. Gehring AJ, Ho ZZ, Tan AT, et al. Profile of tumor antigen-specific CD8 T cells in patients with hepatitis B virus-related hepatocellular carcinoma. *Gastroenterology*. 2009;137(2):682–690. doi:10.1053/j.gastro.2009.04.045
41. Chraa D, Naim A, Olive D, Badou A. T lymphocyte subsets in cancer immunity: friends or foes. *J Leukoc Biol*. 2019;105(2):243–255. doi:10.1002/JLB.MR0318-097R
42. Jiang Y, Tu X, Zhang X, et al. Nutrition and metabolism status alteration in advanced hepatocellular carcinoma patients treated with anti-PD-1 immunotherapy. *Support Care Cancer*. 2020;28(11):5569–5579. doi:10.1007/s00520-020-05478-x
43. Yang M, Song X, Zhang F, et al. Spatial proteomic landscape of primary and relapsed hepatocellular carcinoma reveals immune escape characteristics in early relapse. Hepatology. June 20, 2024.
44. Wang PC, Hu ZQ, Zhou SL, et al. The spatial distribution of immune cell subpopulations in hepatocellular carcinoma. *Cancer Sci*. 2022;113(2):423–431. doi:10.1111/cas.15202
45. Liu X, Zhang K, Kaya NA, et al. Tumor phylogeography reveals block-shaped spatial heterogeneity and the mode of evolution in hepatocellular carcinoma. *Nat Commun*. 2024;15(1):3169. doi:10.1038/s41467-024-47541-9