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ORIGINAL RESEARCH

Comparison of the Prognostic Value of Inflammation-Based Scores in Patients with Hepatocellular Carcinoma After Anti-PD-1 Therapy

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Background: Inflammatory response is related to cancer progression and patient survival. However, the value in predicting survival in hepatocellular carcinoma (HCC) patients who received anti-PD-1 therapy has not been elucidated. This study aimed to compare the predictive ability of inflammation-based scores for the prognosis of HCC patients after anti-PD-1 therapy.

Methods: A total of 442 patients who received anti-PD-1 therapy were included in the study. Representative inflammation-based prognostic scores, including the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-C-reactive protein (CRP) ratio (LCR), lymphocyte-to-monocyte ratio (LMR), systemic immune inflammation index (SII), CRP-to-albumin ratio (CAR), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), and prognostic index (PI), were assessed for prediction accuracy using Kaplan–Meier survival curves, time-dependent receiver operating characteristic (ROC) and Harrell's concordance index (C-index) analyses.

Results: All the inflammation-based prognostic scores exhibited good discriminatory ability in overall survival (OS) (all $P < 0.01$), while the PNI score was a unique independent predictor for OS in multivariate analysis (hazard ratio, 1.770; confidence interval, 1.309–2.393; $P < 0.001$). The areas under the ROC curves at 6, 12, 18 and 24 months and the C-index (0.65) demonstrated that the predictive accuracy of the PNI score was superior to that of the other inflammation-based scores.

Conclusion: The PNI score is a discriminatory prognostic indicator for OS in HCC patients with anti-PD-1 therapy and is superior to the other inflammation-based prognostic scores in terms of predictive ability.

Keywords: inflammation-based score, hepatocellular carcinoma, anti-PD-1 therapy, overall survival, prognostic nutritional index

Introduction

Hepatocellular carcinoma (HCC) is the most common types of liver cancer and the third leading cause of cancer-related deaths worldwide.[1] Due to its uneventful onset and rapid progression, most patients with HCC fail to meet the criteria for radical resection.[2] In recent years, research on programmed cell death protein-1 (PD-1) inhibitors has continued to emerge, offering new treatment models for HCC patients.[3] Given that nivolumab and pembrolizumab have shown certain efficacy and safety, anti-PD-1 therapy is commonly used as a treatment option for systemic

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therapy.[4,5] However, the efficacy of immunotherapy varies greatly among individuals. Practical and reliable prognostic predictors are needed in anti-PD-1 treatment.

Inflammation is a hallmark of cancer.[6] Emerging evidence shows that the host inflammatory response is related to cancer progression and patient survival.[7,8] In immunotherapy, inflammation has a predominant role in tumor survival and proliferation, angiogenesis and immunosuppression.[9] Recently, many inflammation-based prognostic scores composed of systemic inflammatory response factors, including platelet-to-lymphocyte ratio (PLR),[10] neutrophil-to-lymphocyte ratio (NLR),[11] lymphocyte-to-C-reactive protein (CRP) ratio (LCR),[12] lymphocyte-to-monocyte ratio (LMR),[13] systemic immune inflammation index (SII),[14] CRP-to-albumin (ALB) ratio (CAR),[15] prognostic nutritional index (PNI),[16] Glasgow Prognostic Score (GPS),[17] modified Glasgow Prognostic Score (mGPS),[18] and prognostic Index (PI),[19] were proposed to exhibit good predictive ability in cancer prognosis. High pre- and post-treatment NLR and PLR was reported to be associated with worse tumor response and increasing risk of death for anti-PD-1 treatment in HCC.[20] Though, the value of inflammation-based scores in predicting survival after anti-PD-1 treatment in HCC patients has not been fully elucidated.

Herein, this study aimed to make a direct comparison of the prognostic value of various inflammation-based scores in HCC patients after anti-PD-1 therapy.

Materials and Methods

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. The analysis of patient data was reviewed and approved by the Institutional Review Board and Human Ethics Committee at the Sun Yat-sen University Cancer Center (SYSUCC; Guangzhou, China, B2020-190-01).

Patients

Between July 2018 and December 2019, patients diagnosed with HCC who received anti-PD-1 therapy at SYSUCC were screened for eligibility. Patients were included based on the following criteria: (a) diagnosed with HCC through imaging or pathology according to the American Association for the Study of Liver Diseases (AASLD) practice guidelines;[21] (b) had confirmed records of receiving PD-1 inhibitors; (c) aged from 18 to 75 years; (d) had a performance status (PS) score less than 2 and a Child-Pugh (CP) stage of A or B; (e) had no other malignant tumors; and (f) had complete medical and follow-up data. All laboratory serum test data were collected within 3 days before the initial use of PD-1 inhibitors. Imaging evaluation included enhanced computed tomography (CT) or magnetic resonance imaging (MRI) examination within a week before the administration of anti-PD-1 therapy.

Treatment Procedure

PD-1 inhibitors were administered intravenously with saline. The types and dosages of drugs are summarized in Table S1. PD-1 inhibitors could be combined with locoregional interventional therapies or tyrosine kinase inhibitors (TKIs) including sorafenib, lenvatinib, regorafenib or apatinib during treatment. Drug discontinuation was applied upon disease progression, the development of unacceptable toxicity, patient withdrawal of consent, or changes in the treatment plan.

Inflammation-Based Prognostic Scores

The counts of white blood cells, neutrophils, lymphocytes, monocytes, and platelets and the levels of CRP and ALB were obtained through routine laboratory tests of blood samples. The PLR, NLR, LCR, LMR, SII, CAR, GPS, mGPS, PI and PNI were calculated as described in Table 1.

Follow-Up and Definitions

The final follow-up ended on March 31, 2021. Follow-up examinations were conducted using laboratory tests including serum alpha fetoprotein (AFP), liver function, and routine blood tests. Abdominal ultrasonography, enhanced CT or MRI was performed every 1 to 2 months after the receipt of PD-1 inhibitors. Follow-up intervals were routinely 2 to 4 months.

Tumor response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the modified Response Evaluation Criteria in Solid Tumors 1.1 (mRECIST).[22] Overall survival (OS) was defined as the time interval from anti-PD-1 initiation to cancer-related death.

Statistical Analysis

The results are described using the median and range for nonnormally distributed values.

Table 1 Systemic Inflammation-Based Prognostic Scores

Scoring System	Score
Platelet to lymphocyte ratio (PLR)	
Platelet count ($\times 10^9$/L): lymphocyte count ($\times 10^9$/L) < 136.8	0
Platelet count ($\times 10^9$/L): lymphocyte count ($\times 10^9$/L) ≥ 136.8	1
Neutrophil to lymphocyte ratio (NLR)	
Neutrophil count ($\times 10^9$/L): lymphocyte count ($\times 10^9$/L) < 3.3	0
Neutrophil count ($\times 10^9$/L): lymphocyte count ($\times 10^9$/L) ≥ 3.3	1
Lymphocyte to C-reactive protein ratio (LCR)	
$10^4\times$lymphocyte count ($\times 10^9$/L): CRP (mg/L) ≥ 2247.3	0
$10^4\times$lymphocyte count ($\times 10^9$/L): CRP (mg/L) < 2247.3	1
Lymphocyte to monocyte ratio (LMR)	
Lymphocyte count ($\times 10^9$/L): monocyte count ($\times 10^9$/L) ≥ 3.5	0
Lymphocyte count ($\times 10^9$/L): monocyte count ($\times 10^9$/L) < 3.5	1
Systemic Immune-inflammation Index (SII)	
Platelet count ($\times 10^9$/L) × neutrophil count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L) < 268.8	0
Platelet count (×109/L) × neutrophil count (×109/L)/lymphocyte count (×109/L) ≥ 268.8	1
CRP to albumin ratio (CAR)	
CRP (mg/L): albumin (g/L) < 0.1	0
CRP (mg/L): albumin (g/L) ≥ 0.1	1
Glasgow Prognostic Score (GPS)	
CRP ≤10 mg/L and albumin ≥ 35 g/L	0
CRP ≤10 mg/L and albumin < 35 g/L	1
CRP >10 mg/L and albumin ≥ 35 g/L	1
CRP >10 mg/L and albumin < 35 g/L	2
Modified Glasgow Prognostic Score (mGPS)	
CRP ≤10 mg/L and albumin ≥ 35 g/L	0
CRP ≤10 mg/L and albumin < 35 g/L	0
CRP >10 mg/L and albumin ≥ 35 g/L	1
CRP >10 mg/L and albumin < 35 g/L	2
Prognostic Index (PI)	
CRP ≤10 mg/L and WBC count ≤10 × 10^9/L	0
CRP ≤10 mg/L and WBC count >10 × 10^9/L	1
CRP >10 mg/L and WBC count ≤10 × 10^9/L	1
CRP >10 mg/L and WBC count >10 × 10^9/L	2
Prognostic Nutritional Index (PNI)	
Albumin (g/L) + 5 × lymphocyte count ($\times 10^9$/L) ≥ 48	0
Albumin (g/L) + 5 × lymphocyte count ($\times 10^9$/L) < 48	1

Abbreviations: CRP, C-reactive protein; WBC, white blood cell.

Groups were compared by using Student's *t*-test for continuous data and the χ^2 test for categorical data. Survival analysis was performed using the Kaplan-Meier method, and differences in the survival curves were analyzed with the Log rank test. For single value indicators, to avoid deviations from different criteria for the cutoff values of the prognostic scores in this cohort, the optimal cutoff point was calculated using X-tile v.3.6.1 software for PLR, NLR, LCR, LMR, SII, CAR, and PNI (Figure S1). For composite indicators, the GPS, mGPS and PI scores were calculated as generally reported.[17–19] Univariate and multivariate Cox regression analyses were performed to determine prognostic factors for OS. Hazard ratios (HRs) and

confidence intervals (CI) were also calculated. All variables with a P-value < 0.05 in the univariate analyses were used in the multivariate analyses using Cox proportional hazards models. A two-tailed P-value < 0.05 was considered statistically significant. Time-dependent receiver operating characteristic (ROC) curves at 6, 12, 18 and 24 months and the area under the curve (AUC) were calculated to compare the predictive ability of the ten inflammation-based scores. Harrell's concordance index (C-index) was determined to evaluate the predictive ability of the ten inflammation-based scores. All data analyses were performed using SPSS 25.0 software (SPSS Inc., Chicago, IL), GraphPad Prism (version 8.0; GraphPad, Inc.) and R version 4.0.2.

Result

Identification and Characteristics of the Study Patients

From July 2018 to December 2019, a total of 442 patients who received anti-PD-1 therapy and met the criteria were included in the study. Among them, 382 (86.4%) were males. Ages ranged from 21 to 75 years with a median of 52 years. Consistent with the characteristics of HCC in China, 372 (84.2%) patients had hepatitis B. A majority of patients were classified as CP stage A (92.8%) and BCLC stage C (72.2%), and most had multiple tumors (67.9%). A total of 232 (52.5%) patients had macrovascular invasion, and 176 (39.8%) patients had extrahepatic metastasis. The range of tumor size is from 1 to 21.5 cm, with a median of 8.9 cm. The clinical characteristics, including the ten inflammation-based scores of the patients, are summarized in Table 2.

Of note, most patients received another antitumor treatment before anti-PD-1 therapy, including surgery (14.0%), transcatheter arterial chemoembolization (TACE) (20.4%), hepatic infusion chemotherapy (HAIC) (21.0%), ablation (8.1%) and TKIs (11.3%). The duration of anti-PD-1 therapy ranged from 1 to 18.9 months with a median of 5.7 months. The number of treatment cycles ranged from 1 to 25 with a median of 5. The types of PD-1 inhibitors included nivolumab (6.6%), pembrolizumab (7.7%), toripalimab (62.7%), sintilimab (21.3%) and camrelizumab (6.3%) (Table S1). The median duration of follow-up was 13.7 months, while the median OS was 18.3 months. A total of 204 (46.2%) patients died, while 195 (44.1%) patients survived at the end of the follow-up.

Independent Prognostic Factors for OS

Univariate analysis involved prognostic factors related to ethnic characteristics, liver function, tumor burden, the treatment process and the ten inflammation-based scores.

In addition to liver function and tumor stage, all ten inflammation scores were identified as significant prognostic factors for OS. Multivariate analysis revealed that total bilirubin (TBIL) (P = 0.025), Barcelona Clinic Liver Cancer (BCLC) stage (P = 0.003), largest tumor size (P < 0.001), tumor number (P = 0.001) and PNI (P < 0.001) were independent prognostic factors for OS (Table 3).

Overall Survival

As shown in Figure 1, all inflammation-based scores were associated with the OS of patients who received anti-PD-1 therapy. High PLR, NLR, LCR, LMR, SII, CAR, GPS, mGPS, PI and PNI scores indicated poor prognosis (all P < 0.01). However, only the PNI score remained significant in multivariate analysis. The PNI score differentiated the HCC patients into two groups with distinct prognoses (6-, 12-, and 24-month OS rates: 90.9%, 71.7%, and 51.5% and 77.6%, 50.7%, and 25.7%, respectively; P < 0.001).

Comparison of the Performance of the Inflammation-Based Scores

Time-dependent ROC curves at 6, 12, 18 and 24 months of OS were formed to compare the performance of the ten inflammation-based scores (Figure S2), and the PNI score was superior to the others. The AUC of the time-dependent ROC curve showed that the PNI score had a better ability to predict OS. Plots of the time-dependent AUC are shown in Figure 2. The C-indexes were calculated, and the values are provided in Table 4. The PNI scores consistently had higher C-index values than the other scoring systems.

Table 2 Baseline Characteristics of the Enrolled Patients

Variables	N = 442
Age, y	52 (21–75)
Gender (male/female)	382/60 (86.4/13.6)
Hepatitis B (no/yes)	372/70 (84.2/15.8)
HBV-DNA copies	382 (0–2.2×10^8)
WBC (10^9/L)	6.4 (2.3–17.2)
ALT, U/L, (≤/>50)	44.0 (5.6–520.3)
AST, U/L, (≤/>40)	56.5 (14.5–893.4)
ALB, g/L, (≤/>35)	40.7 (24.5–52.4)
TBIL, umol/L, (≤/>17.1)	15.0 (4.0–114.3)
CRP, mg/L	11.5 (0.08–263.5)
AFP, ng/mL	683.6 (1.4–121,000.0)
PIVKA-II, mAU/mL	3628.0 (16.0–75,000.0)
Child-Pugh Grade (A/B)	410/32 (92.8/7.2)
BCLC Stage (A/B/C)	39/84/319 (8.8/19.0/72.2)
Largest tumor size, cm	8.9 (1.0–21.5)
Tumor number (1/>1)	142/300 (32.1/67.9)
Macrovessel invasion (no/yes)	210/232 (47.5/52.5)
Extrahepatic metastasis (no/yes)	266/176 (60.2/39.8)
PLR (0/1)	232/210 (52.5/47.5)
NLR (0/1)	277/165 (62.7/37.3)
LCR (0/1)	191/251 (43.2/56.8)
LMR (0/1)	224/198 (50.2/44.8)
SII (0/1)	76/366 (17.2/82.8)
CAR (0/1)	232/210 (52.5/47.5)
GPS (0/1/2)	213/183/46 (48.2/41.4/10.4)
mGPS (0/1/2)	197/199/46 (44.6/45.0/10.4)
PI (0/1/2)	161/241/40 (36.4/54.5/9.0)
PNI (0/1)	229/213 (51.8/48.2)
Cycles of anti-PD-1	4 (1–25)
Previous treatment	
Surgery	62 (14.0)
TACE	90 (20.4)
HAIC	93 (21.0)
Ablation	36 (8.1)
TKIs*	50 (11.3)

Notes: values are presented as the median (range) or n (%). *TKIs include sorafenib, lenvatinib, regorafenib, apatinib.

Abbreviations: HBV, Hepatitis B virus; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; CRP, C-reactive protein; AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte rate; LCR, lymphocyte C-reactive protein rate; LMR, lymphocyte to monocyte ratio; SII, systemic Immune-inflammation Index; CAR, C-reactive protein to albumin ratio; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; PI, prognostic index; PNI, prognostic nutritional index; PD-1, programmed cell death protein 1; TACE, transcatheter arterial chemoembolization; HAIC, hepatic infusion chemotherapy; TKIs, tyrosine kinase inhibitors.

Relationships Between the PNI Score and Clinical Characteristics and Efficacy

The correlations between clinical characteristics and efficacy and the PNI score are shown in Table 5. A high PNI score was associated with worse aspartate aminotransferase (AST) ($P < 0.001$), ALB ($P < 0.001$), TBIL ($P < 0.001$), and Child-Pugh grade ($P < 0.001$); increased CRP ($P < 0.001$) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) ($P = 0.011$); and larger tumor size ($P < 0.001$), multiple lesions ($P = 0.020$), and macrovascular invasion ($P = 0.004$). Tumor response analysis indicated that the objective response rate (ORR) (34.9% vs 21.1%, $P = 0.001$) and disease control rate (DCR) (75.5% vs 59.6%, $P < 0.001$) were higher in the low PNI group.

Discussion

It is widely acknowledged that inflammation-based scores are associated with cancer-specific survival, but the inflammatory biomarkers that best predict prognosis in anti-PD-1 therapy, especially in HCC patients, remains unclear. To the best of our knowledge, this is the first study to comprehensively identify the correlation between inflammation scoring systems and the OS of HCC patients who received anti-PD-1 therapy. Moreover, the PNI score was found to be superior to the other inflammation-based scores in prediction.

HCC is an inflammation-driven carcinoma, for the majority of HCC arises in the context of chronic

Table 3 Univariate and Multivariate Time-Dependent Cox Regression Analyses of the Prognostic Factors for Overall Survival

Variables	Overall Survival					
	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, y (≤/>50)	0.812	0.613–1.076	0.146			
Gender (male/female)	1.159	0.750–1.791	0.507			
Hepatitis B(no/yes)	1.004	0.687–1.467	0.984			
HBV-DNA copies (≤/>10^3)	1.153	0.868–1.532	0.325			
ALT, U/L, (≤/>50)	1.225	0.925–1.622	0.157			
AST, U/L, (≤/>40)	2.058	1.515–2.794	<0.001			
ALB, g/L, (≤/>35)	0.568	0.404–0.800	0.001			
TBIL, umol/L, (≤/>17.1)	1.615	1.210–2.156	0.001	1.406	1.044–1.892	0.025
AFP, ng/mL (≤/>400)	1.596	1.200–2.122	0.001			
PIVKA-II, mAU/mL, (≤/>400)	1.512	1.103–2.073	0.010			
Child-Pugh Grade (A/B)	2.557	1.653–3.955	<0.001			
BCLC stage (A-B/C)	1.469	1.038–2.080	0.030	1.711	1.206–2.437	0.003
Largest tumor size, cm (≤/>10)	2.327	1.754–3.087	<0.001	2.090	1.568–2.787	<0.001
Tumor number (1/>1)	1.846	1.318–2.586	<0.001	1.747	1.246–2.450	0.001
Macrovascular invasion (no/yes)	1.613	1.210–2.150	0.001			
Extrahepatic metastasis (no/yes)	1.341	1.012–1.776	0.041			
Previous treatment (no/yes)	1.021	0.772–1.352	0.883			
Combination therapy (no/yes)	0.735	0.486–1.111	0.144			
PLR (0/1)	1.691	1.276–2.241	<0.001			
NLR (0/1)	1.714	1.292–2.274	<0.001			
LCR (0/1)	1.585	1.185–2.121	0.002			
LMR (0/1)	1.407	1.069–1.852	0.015			
SII (0/1)	2.049	1.315–3.194	0.002			
CAR (0/1)	1.582	1.194–2.097	0.001			
GPS 0 1 2	 Refence 1.420 2.021	 Refence 1.048–1.923 1.323–3.086	 Refence 0.024 0.001			
mGPS 0 1 2	 Refence 1.513 2.127	 Refence 1.114–2.055 1.382–3.272	 Refence 0.008 0.001			

(*Continued*)

Table 3 (Continued).

Variables	Overall Survival					
	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
PI						
0	Refence	Refence	Refence			
1	1.551	1.127–2.134	0.007			
2	2.593	1.592–4.222	<0.001			
PNI	2.153	1.611–2.876	<0.001	1.770	1.309–2.393	<0.001

Note: P-value < 0.05 is statistically significant in both univariate and multivariate analyses.

Abbreviations: HR, hazard rate; CI, confidence interval; HBV, Hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte rate; LCR, lymphocyte C-reactive protein rate; LMR, lymphocyte to monocyte ratio; SII, systemic Immune-inflammation Index; CAR, C-reactive protein to albumin ratio; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; PI, prognostic index; PNI, prognostic nutritional index.

inflammation and within a fibrotic liver.[23,24] Emerging evidence has shown that the inflammatory response is correlated with the efficacy of anti-PD-1 therapy in advanced cancers.[9,25,26] The unique immunobiology of the liver under conditions of fibrosis and chronic inflammation presents an opportunity for therapeutic targeting with immune checkpoint inhibitors, such as PD-1 inhibitors.[24] A study proposed a tumor inflammation signature constructed with 18 genes that accurately predicted the benefit of patients treated with PD-1 inhibitors.[27] However, the practicability of the model is insufficient in clinical practice. For HCC, the NLR and PLR were reported to have strong predictive roles in anti-PD-1 therapy,[20,28,29] which was verified in our study. With the combination of albumin and lymphocytes, our study suggested that the presence of the systemic inflammatory response revealed by PNI was the optimal tool in the assessment of survival in HCC patients treated with PD-1 inhibitors compared with the other inflammation-based scores. The PNI score is measured using an inexpensive, easily available, simplified approach in clinical practice to stratify HCC patients with anti-PD-1 therapy into different risk groups.

The PNI score has been demonstrated to be an effective prognostic predictor in many types of digestive system cancers, including HCC.[30] The underlying mechanism has not been well clarified. In this study, one possible explanation is that the decrease in lymphocytes indicates a weakening of immunity.[31] In addition, the depletion of lymphocytes, such as CD4- and CD8-positive T cells, is the key to immunosuppression.[32] Lymphocytes within the tumor microenvironment seem to be critical in determining the efficacy of immune surveillance and lethality.[33] On the other hand, albumin reflects liver function, which determines the sustainability of immunotherapy and prognosis in HCC patients. Albumin is an indicator of nutritional status. A study indicated that nutrition and metabolism in patients with advanced HCC were closely related to anti-PD-1 treatment efficacy as well as survival benefit.[34] Low serum albumin levels reflect a state of malnutrition, which would weaken cellular and humoral immunity, phagocytic functions, and other defense mechanisms in patients with cancer.[35]

This study has some limitations. First, this was a retrospective study conducted on a single-center cohort in China. A majority of the included patients had hepatitis B-related HCC. Since hepatitis C virus infection, alcohol abuse and an unbalanced diet are the leading causes of HCC in Japan, the United States, and European countries, the results need to be validated in external institutions with different disease backgrounds. Second, we used measures to control the consistency of each inflammation-based score; however, the best cutoff value of PNI in this study is not widely accepted (for the most common cutoff value is 45). If necessary, it should be revalidated and redefined

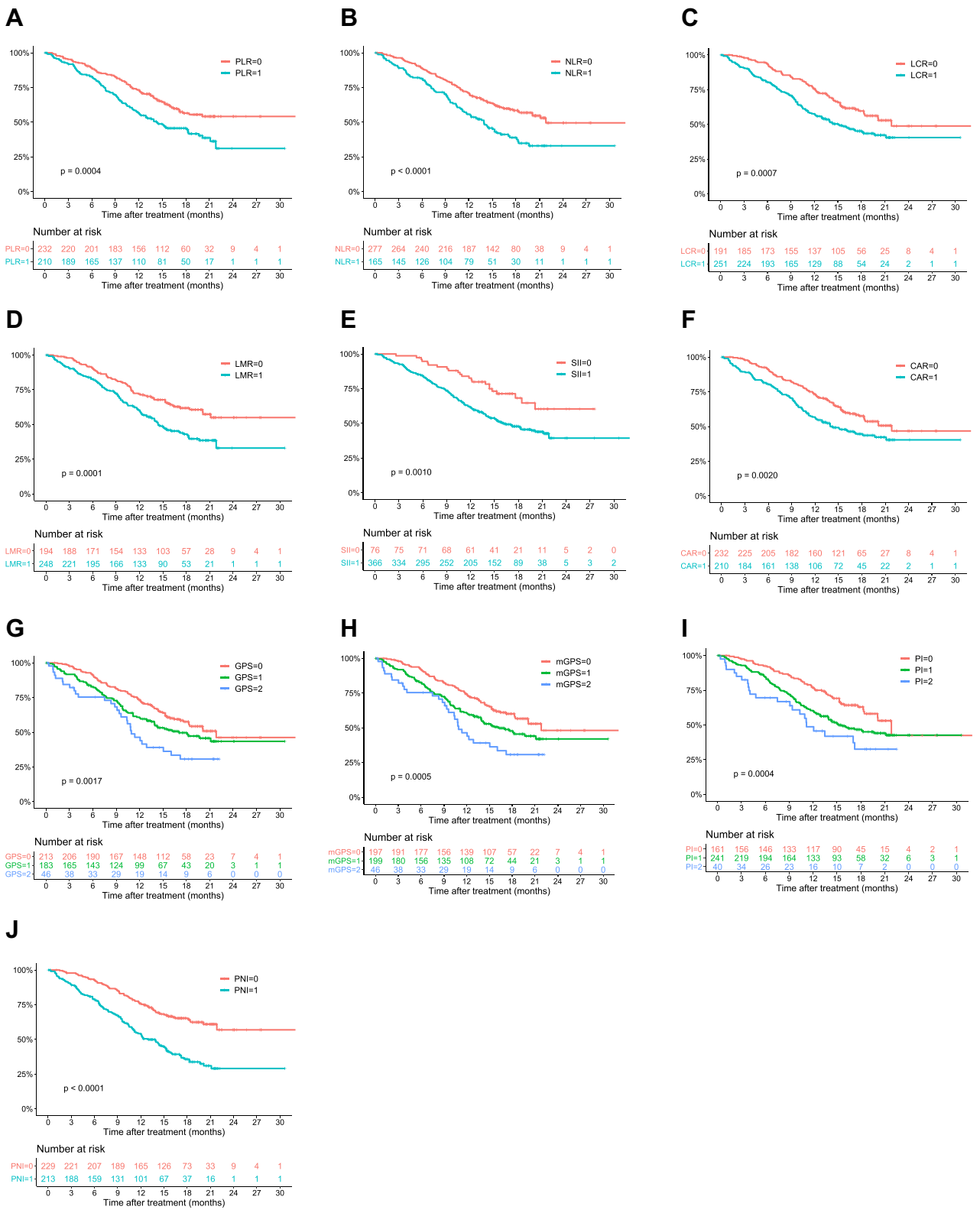

Figure 1 Kaplan-Meier curves of the overall survival of HCC patients after anti-PD-1 therapy. (**A**) PLR, (**B**) NLR, (**C**) LCR, (**D**) LMR, (**E**) SII, (**F**) CAR, (**G**) GPS, (**H**) mGPS, (**I**) PI and (**J**) PNI.

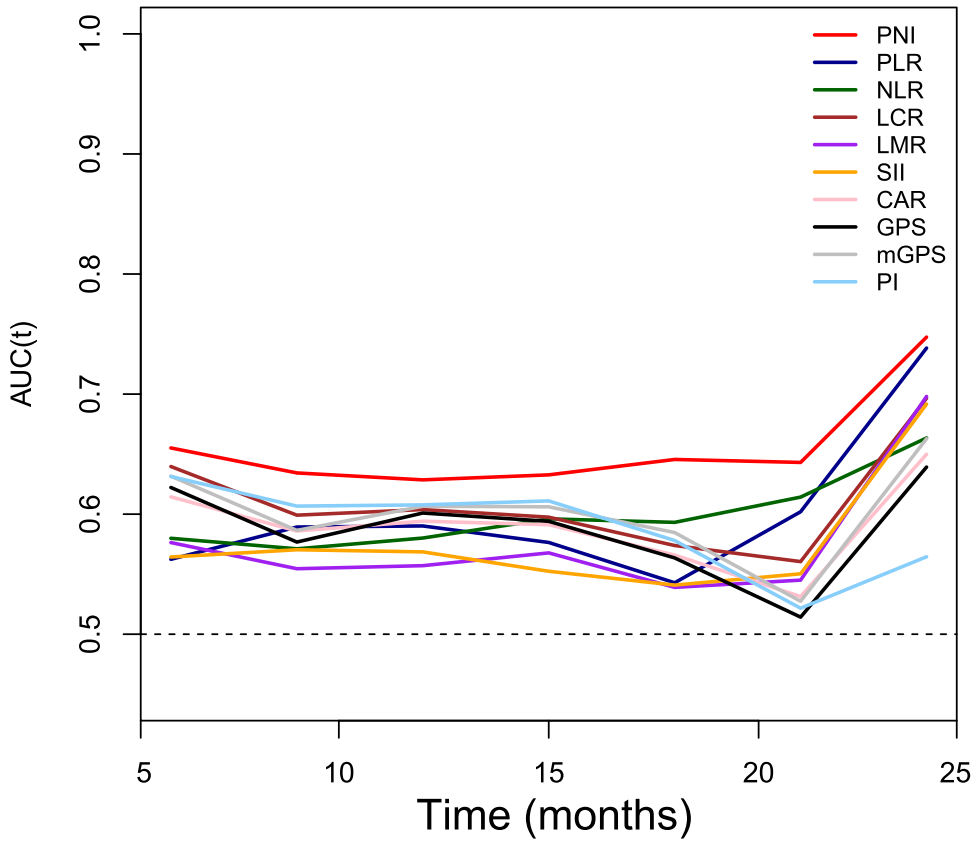

Figure 2 Time-dependent AUC plot for survival prediction of inflammation-based scores.

in future studies with authoritative sources. Third, patients received non-single PD-1 inhibitors during the whole treatment, which inevitably caused bias. Finally, the underlying potential regulatory mechanism of albumin and lymphocytes on immunotherapy has not been elucidated and deserves further investigation.

Conclusions

Our study demonstrated that the PNI score was an independent prognostic indicator in HCC patients receiving anti-PD-1 therapy and performed well compared with the other inflammation-based scores. This is an easy-to-use tool for risk stratification and benefits physicians in the

Table 4 Concordance Index for the Comparison of Different Inflammatory-Based Scores

Scores	6-Month AUROC	12-Month AUROC	18-Month AUROC	24-Month AUROC	C-Index
PNI	0.66 (0.60–0.72)	0.63 (0.57–0.69)	0.65 (0.59–0.70)	0.75 (0.69–0.81)	0.65 (0.62–0.68)
PLR	0.56 (0.49–0.63)	0.59 (0.53–0.65)	0.54 (0.49–0.60)	0.73 (0.66–0.80)	0.59 (0.56–0.62)
NLR	0.58 (0.50–0.66)	0.58 (0.52–0.64)	0.59 (0.53–0.64)	0.66 (0.60–0.72)	0.59 (0.56–0.62)
LCR	0.64 (0.57–0.71)	0.60 (0.55–0.66)	0.58 (0.52–0.63)	0.69 (0.64–0.74)	0.60 (0.57–0.63)
LMR	0.58 (0.50–0.66)	0.56 (0.50–0.61)	0.54 (0.49–0.60)	0.70 (0.56–0.74)	0.57 (0.54–0.60)
SII	0.57 (0.49–0.64)	0.57 (0.51–0.63)	0.54 (0.48–0.60)	0.69 (0.64–0.74)	0.57 (0.55–0.59)
CAR	0.61 (0.53–0.69)	0.60 (0.54–0.65)	0.57 (0.51–0.62)	0.65 (0.59–0.71)	0.59 (0.56–0.62)
GPS	0.62 (0.54–0.69)	0.60 (0.54–0.66)	0.56 (0.50–0.62)	0.64 (0.59–0.70)	0.59 (0.57–0.62)
mGPS	0.63 (0.55–0.70)	0.61 (0.55–0.67)	0.58 (0.52–0.63)	0.66 (0.60–0.72)	0.60 (0.57–0.63)
PI	0.63 (0.56–0.71)	0.61 (0.55–0.67)	0.58 (0.52–0.64)	0.56 (0.51–0.61)	0.60 (0.57–0.63)

Note: values are presented as the AUROC (95% confidence interval).

Abbreviations: AUROC, area under the receiver operating characteristic curve; PNI, prognostic nutritional index; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte rate; LCR, lymphocyte C-reactive protein rate; LMR, lymphocyte to monocyte ratio; SII, systemic Immune-inflammation Index; CAR, C-reactive protein to albumin ratio; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; PI, prognostic index.

Table 5 Baseline Characteristics of the Patients Grouped by PNI Score

Variables	PNI = 0	PNI = 1	*P*
	N = 229	N = 213	
Age, y	50 (23–75)	54 (21–75)	0.009
Gender (male/female)	195/34 (85.2/14.8)	187/26 (87.8/12.2)	0.418
Hepatitis (no/yes)	37/192 (16.2/83.8)	33/180 (15.5/84.5)	0.848
HBV-DNA copies	198 (0–6.7×10^6)	989 (0–2.2×10^8)	0.119
WBC (10^9/L)	6.6 (2.7–15.3)	6.0 (2.3–17.2)	0.864
ALT, U/L, (≤/>50)	40.4 (5.6–520.3)	45.9 (9.1–263.8)	0.187
AST, U/L, (≤/>40)	47.2 (14.5–728.1)	67.9 (17.6–893.4)	<0.001
ALB, g/L, (≤/>35)	43.6 (34.0–52.4)	37.2 (24.5–44.6)	<0.001
TBIL, umol/L, (≤/>17.1)	13.0 (4.0–54.2)	17.1 (4.2–114.3)	<0.001
CRP, mg/L	5.8 (0.08–263.5)	18.7 (0.5–223.4)	<0.001
AFP, ng/mL	418 (1.9–121,000)	1129 (1.4–121,000)	0.218
PIVKA-II, mAU/mL	2246 (19–75,000)	7607 (16–75,000)	0.011
Child-Pugh Grade (A/B)	227/2 (99.1/0.9)	183/30 (85.9/14.1)	<0.001
BCLC Stage (A/B/C)	24/41/164 (10.5/17.9/71.6)	15/43/155 (7.0/20.2/72.8)	0.406
Largest tumor size, cm (≤/>10)	8.0 (1.0–21.5)	10.1 (1.0–20.3)	<0.001
Tumor number (1/>1)	85/144 (37.1/62.9)	57/156 (26.8/73.2)	0.020
Macrovascular invasion (no/yes)	124/105 (54.1/45.9)	86/127 (40.4/59.6)	0.004
Extrahepatic metastasis (no/yes)	131/98 (57.2/42.8)	135/78 (63.4/36.6)	0.185
Cycles of anti-PD-1	5 (1–25)	3 (1–25)	<0.001
Previous treatment			
Surgery	42 (18.3)	20 (9.4)	0.007
TACE	49 (21.4)	41 (19.2)	0.575
HAIC	39 (17.0)	54 (25.4)	0.032
Ablation	26 (11.4)	12 (5.6)	0.032
TKIs*	28 (12.2)	22 (10.3)	0.529
Best tumor response**			
CR	11 (4.8)	6 (2.8)	0.278
PR	69 (30.1)	39 (18.3)	0.004
SD	93 (40.6)	82 (38.5)	0.708
PD	33 (14.4)	38 (17.8)	0.326
NA	23 (10.1)	48 (22.5)	0.001
ORR	80 (34.9)	45 (21.1)	0.001
DCR	173 (75.5)	127 (59.6)	<0.001

Notes: values are presented as the median (range) or n (%). P-value < 0.05 is statistically significant. *TKIs include sorafenib, lenvatinib, regorafenib, apatinib. **Tumor response were evaluated according to mRESIST criterion.

Abbreviations: PNI, prognostic nutritional index; HBV, Hepatitis B virus; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; CRP, C-reactive protein; AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte rate; LCR, lymphocyte C-reactive protein rate; LMR, lymphocyte to monocyte ratio; SII, systemic Immune-inflammation Index; CAR, C-reactive protein to albumin ratio; GPS, Glasgow prognostic score; mGPS, modified Glasgow prognostic score; PI, prognostic index; PD-1, programmed cell death protein 1; TACE, transcatheter arterial chemoembolization; HAIC, hepatic infusion chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessed; ORR, objective response rate; DCR, disease control rate; TKIs, tyrosine kinase inhibitors.

selection of therapeutic strategies for anti-PD-1 treatment in HCC patients.

Data Sharing Statement

The data are available from the Sun Yat-sen University Cancer Center Institutional Data Access/Ethics Committee for researchers. The data sets used during the present study are available from the corresponding authors on reasonable request.

Ethics Approval Statement

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. This research was approved by the institutional review board of Sun Yat-sen

University Cancer Center (RDDA2020001831). Patient informed consent is exempt because the study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment. Individuals cannot be identified based on the data presented. We declare to ensure the confidentiality of patient data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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