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Prognostic value of inflammation-immunity-nutrition score in patients with hepatocellular carcinoma treated with anti-PD-1 therapy

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Abstract

Background: There are no validated biomarkers that can predict the clinical benefit of immune checkpoint blockers against the programmed cell death protein 1 (PD-1) treatments in hepatocellular carcinoma (HCC). This study aimed to investigate the prognostic value of inflammation-immunity-nutrition score (IINS) in patients with HCC treated with anti-PD-1 therapy.

Methods: A consecutive series of 101 HCC patients treated with PD-1 inhibitors in Sichuan Provincial People's Hospital between January 2018 and August 2020 were enrolled in the retrospective study. IINS (0–6) was constructed based on pretreatment high-sensitivity C-reactive protein (hsCRP), lymphocyte (LYM), and albumin (ALB). The patients were divided into high and low IINS groups according to IINS values. Prognostic values of each variable were evaluated with univariate and multivariate time-dependent Cox regression analyses. Survival curves were calculated and compared using the Kaplan–Meier method and log-rank test. The prognostic performance of IINS was further compared with that of other traditional prognostic indicators by receiver operating characteristic (ROC) curve and the areas under the ROC curve.

Results: Patients with low IINS had longer overall survival (OS) (HR: 4.711, 95% CI: 1.80–12.37, $p = .001$) and progression-free survival (HR: 3.411, 95% CI: 1.79–6.51, $p < .0001$) than those with high IINS. The multivariate analysis identified IINS (HR: 3.746, 95% CI: 1.05–13.38, $p = .042$) and tumor number (HR: 5.111, 95% CI: 1.075–24.299, $p = .04$) as independent prognostic factors. According to ROC analysis, IINS (AUC =0.729, 95% CI: 0.597–0.861, $p = .002$) presented better prognostic performance than other traditional prognostic indicators. The area of the IINS-CA19-9 under the ROC curve (AUC) was higher than that of the IINS or CA19-9 levels for the prediction of OS.

Conclusion: The results suggest that IINS may be an independent prognostic indicator for HCC patients treated with anti-PD-1 therapy. IINS-CA19-9 classification may be more effective in predicting clinical benefit of anti-PD-1 therapy in HCC patients.

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1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer death worldwide in 2020, with approximately 906,000 new diagnosed cases and 830,000 deaths.[1] Due to its inapparent symptoms and rapid progression, the majority of HCC patients are diagnosed with advanced stage disease, resulting in failing to radical resection and available HCC treatments merely palliative.[2] Within a decade, immunotherapy targeting immune checkpoints for HCC have grown dramatically and changed the treatment paradigm. Immune checkpoint blockers against PD-1 and cytotoxic T lymphocyte antigen 4 have been approved for HCC in second-line treatment, with persisting clinical responses and prolonging survival.[3] However, because of the efficacy of PD-1 inhibitors varying greatly among individuals, as well as the unsustainable cost burden and immune-mediated toxicities associated with anti-PD-1 therapy, practical and reliable prognostic predictors are urgently need to identify HCC patients who are likely to benefit from anti–PD-1 therapy.

In immunotherapy, inflammation and innate immunity have a vital role in tumorigenesis, angiogenesis, and immunosuppression. Evidence increasingly suggests that host inflammatory response and immune function are associated with cancer progression and patient survival.[4] Several studies have evaluated that inflammation-based prognostic scores such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) are predictive biomarkers in patients with HCC treated with anti-PD-1 therapy, and higher NLR, PLR, and PNI at baseline are associated with shorter OS and treatment failure.[5,6]

High-sensitivity C-reactive protein (hsCRP) is the most sensitive protein for the detection of systemic inflammation and is also correlated with the prognosis in HCC.[7–9] Lymphocyte (LYM) and albumin (ALB), as two essential components of the inflammation-based prognostic scores, reflect the systemic immune and nutritional status, respectively. ALB is also closely related to the nutrition and metabolism of cancer patients and their prognosis.[10,11] Studies have shown that prognostic scores derived from the combination of several of hsCRP, LYM, and ALB were constructed, such as hsCRP/ALB, hsCRP/LYM, PNI, and were superior to individual indicators in terms of predictive ability.[6,8,9] As a result, Li et al. initiated that inflammation-immunity-nutrition score (IINS), which was simply based on hsCRP, LYM, and ALB, might be prognostic predictor for patients with resectable colorectal cancer, and high IINS presented treatment failure and poor prognosis.[12] However, the prognostic role of IINS in HCC patients treated with anti-PD-1 therapy has not been evaluated. Therefore, this study evaluated the prognostic value of IINS on survival outcomes in patients with HCC treated with anti-PD-1 therapy using real-world data.

2 | MATERIALS AND METHODS

2.1 | Study population

This study enrolled 101 patients who was diagnosed as HCC and treated with PD-1 inhibitors in Sichuan Provincial People's Hospital between January 1, 2018 and August 31, 2020. Patients were included based on the following criteria: diagnosed with HCC confirmed by pathology; no therapy for primary HCC; had confirmed records of receiving PD-1 inhibitors; aged from 18 to 75 years; had no other malignant tumors, cardiovascular, and cerebrovascular diseases; and had complete medical and follow-up data. The exclusion criteria were as follows: having history of malignant tumors or concurrent other malignant tumors; having diseases of the hematologic system; having missing information on hsCRP level, serum ALB level, or LYM counts; Child–Pugh grade D; pre-existing stress response and inflammatory conditions, such as active or chronic infection; lost to follow-up within 1 months after anti-PD-1 therapy. The flow chart of the study design is showed in Figure 1.

The study protocol was approved by Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital ethics committee (NO2021-447). Informed consent was obtained from all patients and subjects.

2.2 | Data collection

Complete blood parameters of all patients were collected on the day of admission. Prior to receiving PD-1 inhibitors, those patients received different treatments according to their condition in our hospital, including surgery, transcatheter arterial chemoembolization, hepatic infusion chemotherapy, chemotherapy, and tyrosine kinase inhibitors. Demographic, clinical, and image data were also collected. In addition, according to the response evaluation criteria in solid tumors (RECIST 1.1), tumor assessment and responses to anti-PD-1 treatment were performed and classified at baseline and then after every two treatment cycles, which was generally after every 6 weeks. The last follow-up was on August 31, 2021.

2.3 | Calculation

According to the association between each indicators and the patients' OS, the optimal cutoff points of hsCRP, LYM, and ALB using X-tile software version 3.6.1 (https://medicine.yale.edu/lab/rimm/research/software/) for survival prediction was determined. Based on 2 cutoffs, hsCRP was divided into three

Patients were diagnosis as HCC and treated with PD-1
inhibitors in Sichuan Provincial People's Hospital (N=158)

Patients received different treatments
according to their condition (N=158)

Excluded 57 individuals:
(1) having history of malignant tumors or concurrent
    other malignant tumors; (N=10)
(2) no diseases of the hematologic system; (N=18)
(3) having missing information on hsCRP level, serum
    ALB level, or LYM counts; (N=5)
(4) Child-Pugh grade D; (N=2)
(5) preexisting stress response and inflammatory
    conditions, such as active or chronic infection; (N=5)
(6) lost to follow-up within 1 months after anti-PD-1
    therapy. (N=17)

101 patients were included

IINS ≦ 3 (N=66)
Cancer progression (N=19)
Death (N=7)

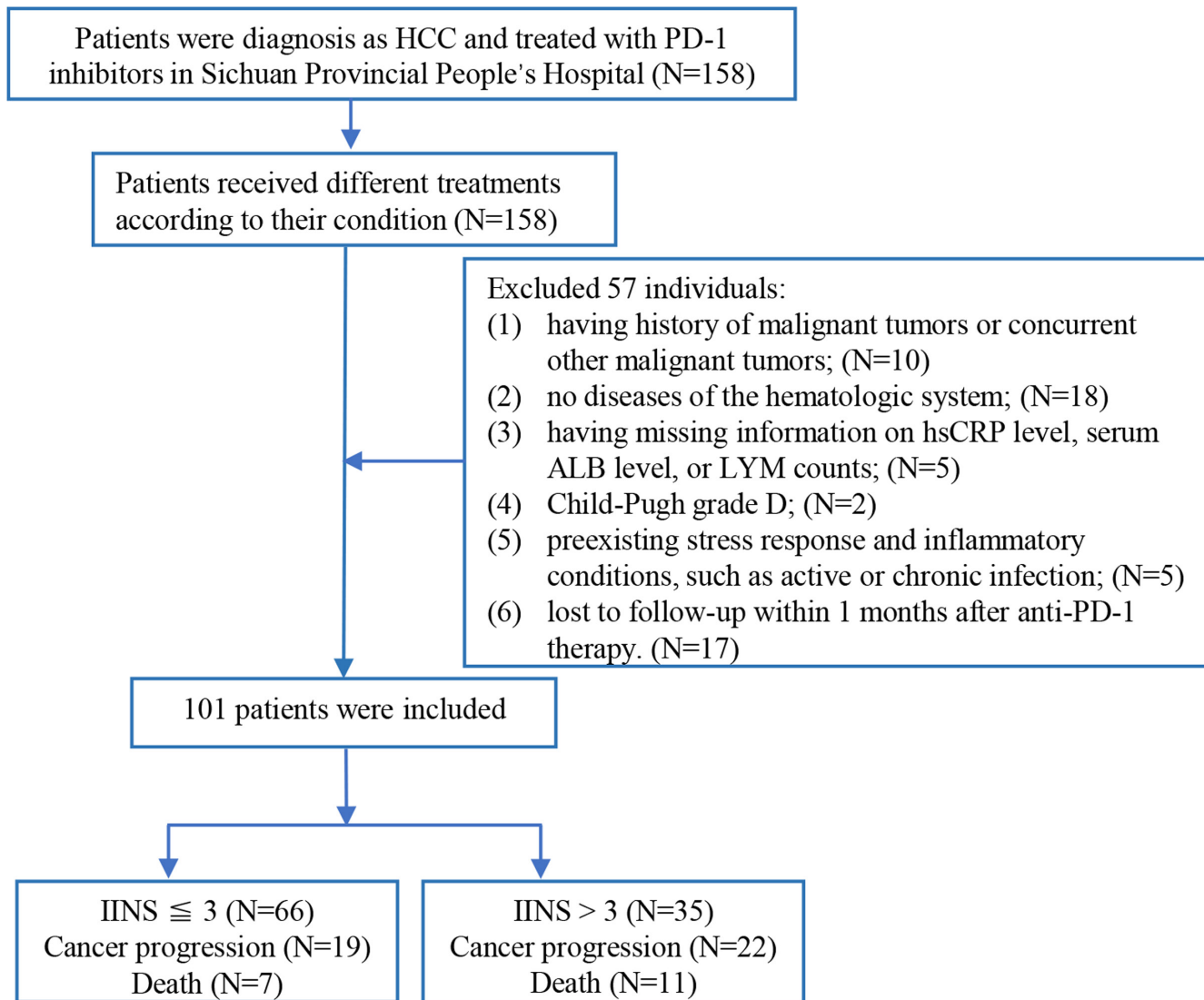IINS > 3 (N=35)
Cancer progression (N=22)
Death (N=11)

FIGURE 1 Flow chart of the study design. HCC, hepatocellular carcinoma; PD-1, programmed cell death protein 1; hsCRP, high-sensitivity C-reactive protein; ALB, albumin; LYM, lymphocyte; IINS, inflammation-immunity-nutrition score

groups: score 0: ≤2.8 mg/L, score 1: >2.8 mg/L and ≤34.3 mg/L, and score 2: >34.3 mg/L, whereas the classification of LYM and ALB was as follows: LYM (score 0: >1.18 × 10^9/L, score 1: >0.91 × 10^9/L and ≤1.18 × 10^9/L, and score 2: ≤0.91 × 10^9/L); ALB (score 0: >37.7 g/L, score 1: >33.5 g/L and ≤37.7 g/L, and score 2: ≤33.5 g/L) (Supplemental Figure 1). Then, the inflammation-immunity-nutrition score (IINS) was generated by summing the scores of hsCRP, LYM, and ALB. In our study, since the median of IINS was 3, the patients were divided into two groups: IINS ≦3 was defined as low IINS group, and IINS >3 was high IINS group, respectively.

2.4 | Statistical analysis

Overall survival (OS) defined as the interval from the first PD-1 inhibitor treatment until death or still alive at the last follow-up.

Progression-free survival (PFS) was calculated from treatment until disease progression (PD), death, or the last follow-up (censored). Based on RECIST ver.1.1, the objective response rate (ORR) was the number of patients with complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as the proportion of patients with CR, PR, or stable disease (SD).

The clinical characteristics of patients were compared using the Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Continuous and categorical variables were expressed as mean [standard deviation (SD)] and proportions (percentages), respectively. Multivariate time-dependent Cox proportional PFS and OS hazard ratios (HRs) were fitted based on significant univariate factors. Survival analyses were performed using the Kaplan–Meier method and Log rank test. All P values were from two-sided tests. All data analyses were performed using SPSS version 27.0 (IBM Corp.,) and GraphPad Prism version 9.2.0 (GraphPad,).

3 | RESULTS

3.1 | Patient characteristics

A total of 101 patients included in the study, 84 (83.2%), were men, and the median (interquartile ranges, IQRs) age of all patients was 55 (49–63) years. Fifty-nine (58.4%) patients has hepatitis B virus infection, and the median (IQR) HBV-DNA copies of whom was 50244.83 (0–249.5) IU/ML. Most patients received another antitumor treatment before anti-PD-1 therapy, including surgery (36.6%), transcatheter arterial chemoembolization (TACE) (13.6%), hepatic infusion chemotherapy (HAIC) (19.7%), chemotherapy (9.9%), and tyrosine kinase inhibitors (TKIs) (5%). Forty-eight (45.5%) patients were treated with PD-1 monotherapy, and 65 (54.5%) patients were treated with PD-1 inhibitors simultaneously combined with targeted therapy. The most frequently used PD-1 inhibitor was camrelizumab (68.3%). Category and dosage of PD-1 inhibitors used in the two groups are shown in Table S1. The patients with high IINS were more likely to have higher Child–Pugh grade and advanced BCLC Stage, higher hsCRP (mean: 45.76 mg/L), and serum CA19-9 levels (mean: 1277.37 U/ml), but lower ALB (mean: 31.97 g/L) and LYM (mean: 0.87×10^9/L) levels. The baseline characteristics of the patients are listed in Table 1.

3.2 | Treatment response and survival

The median follow-up time was 11.1 m (95% CI: 3–22.0). The median PFS was 7 m (95% CI: 1.3–22.0), and median OS was 10 m (95% CI: 2–22.0). As summarized in Table 2, no patients achieved complete response, 31 patients (30.7%) achieved partial response, 26 patients (25.7%) had SD, and 42 patients (41.6%) had PD. ORR was 30.7%, and DCR was 56.4%. Low IINS group achieved higher ORR (low vs high IINS, 83.9% vs 16.1%; $p = .019$), and DCR (low vs high IINS, 48.5% vs 7.9%; $p < .001$) from anti-PD-1 treatment compared with high IINS group. At the end of follow-up, 41 (40.59%) patients presented cancer progression, and 18 (17.82%) patients died. Moreover, high IINS group presented increasing cancer progression ($p = .001$) and death risk ($p = .009$) compared with low IINS group (Table 1).

3.3 | The association between Inflammation-Immunity-Nutrition Score and OS

In univariate analysis, IINS ($p = .001$), tumor number ($p = .037$), Child–Pugh stage C ($p = .041$), BCLC stage D ($p = .007$), extrahepatic metastasis ($p = .041$), cycles of anti-PD-1 ($p = .001$), and combination with target therapy ($p = .005$) were all significantly associated with OS. Multivariate analysis revealed that high IINS was associated with significant worse OS, with the multi-variable-adjusted hazard ratio (HR) (95% CI) of 3.746 (1.049–13.379, $p = .042$), and tumor number ($p = .04$) were also independent prognostic factors (Table 3). There was no statistical significance between different category of PD-1

inhibitors by univariate analysis (Table S2). The complete information from univariate analysis is listed in Table S3. High IINS was associated with significantly worse OS compared with low IINS (HR 4.711, 95% CI, 1.8–12.4, $p = .001$) (Figure 2A). In the high IINS and low IINS groups, the median survival was 16.3 months (95% CI, 1.24–22.8) and not reached (95% CI, 2–21.65), respectively.

3.4 | The association between Inflammation-Immunity-Nutrition Score and PFS

In univariate analysis, IINS ($p < .0001$), BCLC Stage D ($p = .019$), extrahepatic metastasis ($p = .007$), serum ALB (≥35:<35) ($p = .031$), CA19-9 levels ($p = .002$), cycles of anti-PD-1 ($p = .001$), and combination with targeted therapy ($p = .021$) were significantly associated with PFS. In multivariate analysis, high IINS emerged as the powerful unfavorable prognostic factor of PFS (HR: 3.850; 95% CI: 1.007–14.727; $p = .049$) (Table 4). The complete information from univariate analysis is listed in Table S4. Low IINS was associated with a significantly longer PFS compared with high IINS (HR: 3.411; 95% CI: 1.787–6.512, $p < .0001$) (Figure 2B). The median PFS was 18.8 (95% CI, 3–23.95) months and 11.5 (95% CI, 4–18.6) months in the low and high IINS groups, respectively.

3.5 | Relationships between IINS-CA19-9 classification and the prognosis of patients

In our study, similar to IINS groups, with the cutoff values of carbohydrate antigen 19–9 (CA19-9) (cutoff =18.31), we found patients in the low CA19-9 group (CA19-9≤18.31) had a longer OS compared with patients in the high CA19-9 group (CA19-9>18.31) (HR:5.799, 95% CI:2.235–15.05; $p < .0001$, Figure 3A), and longer PFS (HR:1.874, 95% CI:1.023–3.435; $p < .05$, Figure 3B), respectively. Then, according to IINS-CA19-9 classification, patients were divided into different groups as follows: patients with low IINS and low CA19-9 were group I, patients with high IINS and low CA19-9 or with low IINS and high CA19-9 were group II, and patients with high IINS and high CA19-9 were group III. Group I had a longer OS ($p < .0001$, Figure 4A) and PFS ($p < .0001$, Figure 4B) compared with group II and III.

3.6 | Comparing the prognostic values of inflammation-immunity-nutrition score with other traditional indicators

To compare the prognostic predictive performance of IINS with other traditional indicators, including Child–Pugh grade, α-fetoprotein (AFP), NLR, PLR, hsCRP/ALB, hsCRP/LYM, and PNI, the AUCs (95% CIs) of the indicators were calculated. ROC analysis was used to further evaluate the effect of these indicators on prognosis in our research. Our results showed that IINS presented better performance for OS in

TABLE 1 Demographic and clinical characteristics of the enrolled patients (N = 101)

Characteristics	Overall (n = 101)	IINS (0–6) IINS≤3 (n = 66)	IINS>3 (n = 35)	p value
Gender (male/female)	84 (83.2)/17 (16.8)	54 (81.82)/12 (18.18)	30 (85.71)/5 (14.29)	.618
Age (years) median (IQR)	55 (49–63)	55 (48–63)	57 (52–64)	.872
BMI (kg/m^2) median (IQR)	22.04 (20.5–24)	22.24 (20.4–24.22)	21.80 (20.57–23.5)	.327
Etiology (HBV/HCV/Other)	59 (58.4)/2 (2)/40 (39.6)	40 (60.61)/1 (1.52)/22 (33.33)	19 (54.29)/1 (2.86)/ 17 (48.57)	.483
HBV-DNA copies median (IQR)	50244.83 (0–249.5)	25205.78 (0–166)	106912.13 (0–1090)	.549
Liver cirrhosis (no/yes)	49 (48.5)/52 (51.5)	30 (45.45)/36 (54.55)	19 (54.29)/16 (45.71)	.398
Child–Pugh grade				.014
A	57 (56.44)	44 (66.67)	13 (37.14)	
B	40 (39.6)	21 (31.82)	20 (54.29)	
C	4 (3.96)	1 (1.52)	2 (8.57)	
BCLC Stage				.049
B	61 (60.4)	44 (66.67)	17 (48.57)	
C	35 (34.65)	21 (31.82)	14 (40)	
D	5 (4.95)	1 (1.52)	4 (11.43)	
Largest tumor size (cm)	7.23 (3.59)	7.19 (3.53)	7.31 (3.76)	.923
Tumor number (Single/ Multiple)	41 (40.59)/60 (59.41)	27 (40.91)/39 (59.09)	14 (40)/21 (60)	.929
Macrovascular invasion (no/yes)	68 (67.33)/33 (32.67)	47 (71.21)/19 (28.79)	21 (60)/14 (40)	.253
Extrahepatic metastasis (no/yes)	59 (58.42)/42 (41.58)	41 (40.59)/25 (59.41)	18 (51.43)/17 (48.57)	.299
ALB (g/L)	35.8 (32.5–39.1)	37.85 (3.85)	31.97 (4.14)	<.0001
AFP (ng/mL)	7226.29 (25101.55)	8171.03 (27113.83)	5444.78 (21041.52)	.687
CA19-9 (U/mL) (≤/>18.31)	11 (5.59)/1010.47 (3091.05)	7.45 (5.18)/114.01(4741.04)	7.06 (5.14)/10.9 (3242.30)	.019
Lymphocyte (10^9/L)	1.3 (1.58)	1.53 (1.89)	0.87 (0.43)	<.0001
hsCRP, mg/L	26.69 (44.41)	16.57 (31.43)	45.76 (57.78)	.001
Cycles of anti-PD-1	10.1 (7.25)	10.95 (7.61)	8.49 (6.3)	.12
Previous treatment				.122
Surgery	37 (36.63)	28 (42.42)	9 (25.71)	
TACE	22 (21.8)	9 (13.64)	13 (37.14)	
HAIC	21 (20.8)	13 (19.70)	8 (22.86)	
Chemotherapy	10 (9.9)	4 (6.06)	6 (17.14)	
TKIs	5 (5.0)	3 (4.55)	2 (5.71)	
Combined with target therapy (no/yes)	46 (45.54)/65 (54.46)	27 (40.91)/49 (59.09)	19 (54.29)/16 (45.71)	.062
Cancer progression, n (%) (no/yes)	60 (59.41)/41 (40.59)	47 (71.21)/19 (28.79)	13 (37.14)/22 (62.86)	.001
Death, n (%) (no/yes)	83 (82.18)/18 (17.82)	59 (89.39)/7 (10.61)	24 (68.57)/11 (31.43)	.009

Abbreviations: AFP, alpha fetoprotein; ALB, albumin; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; CA19-9, carbohydrate antigen 19–9; HAIC, hepatic infusion chemotherapy; HBV, hepatitis B virus; HCV, hepatitis C virus; hsCRP, high-sensitivity C-reactive protein; IINS, inflammation-immunity-nutrition score; IQRs, interquartile ranges; PD-1, programmed cell death protein 1; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors.

HCC patients treated with anti-PD-1 therapy than other traditional indicators (AUC =0.729, 95% CI: 0.597–0.861, specificity =0.722, sensitivity =0.735, p = .002; Table 5, Figure 5A). We further evaluate the effect of IINS-CA19-9 classification on prognosis in our research. The ROC analysis showed that the pretreatment IINS-CA19-9 scores were more predictive of OS than IINS or serum CA19-9 levels alone (AUC =0.764, 95% CI: 0.631–0.897, p = .001; Figure 5B).

4 | DISCUSSION

Programmed cell death protein 1 (PD-1) inhibitors have emerged as an effective therapeutic approach for hepatocellular carcinoma (HCC), associating with a curable potential and a durable survival due to a substantial heterogeneity, and only a small proportion of HCC patients could benefit from anti-PD-1 therapy, resulting in

a low objective response rate (ORR) of 10%–25%.[13] Tumor mutational burden, microsatellite instability, PD-L1 expression level, the number of tumor-infiltrating lymphocytes, and gene expression characteristics have been evaluated as effective measures to predict treatment response and improve cancer patients' prognosis, including melanoma, colon cancer, and non-small cell lung cancer, while the improvement of HCC patients' prognosis has still remained a main clinical challenge.[13–15] In addition, because of the unavailability of tumor tissues and complex molecular or microscopic analyses, these possible biomarkers have a limited predictive accuracy, and are not practically utilized in clinic.[16] Therefore,

it is vital to explore practical and reliable biomarkers that can predict treatment outcomes.

A simple and novel serum biomarker, inflammation-immunity-nutrition score (IINS), which is based on hsCRP, LYM, and ALB, was proposed by Li et al. and reported to play strong predictive roles in prognostic outcome for patients with resectable colorectal cancer (CRC). A high IINS was associated with the worse survival of CRC.[12] Furthermore, IINS might serve as an ideal biomarker because of being easily accessible, noninvasive, and cost-effective.

Similarly, recent studies have suggested that pretreatment neutrophil-to-lymphocyte ratio, mutational burden, lung immune prognostic index (LIPI), and inflammation-based prognostic scores were associated with clinical outcomes and clinical benefits in HCC patients treated with PD-1 inhibitors.[5,15,17,18] The latest research also suggests that in terms of predictive ability, the PNI score is a discriminatory prognostic indicator for OS in HCC patients with anti-PD-1 therapy and was superior to the other inflammation-based prognostic scores, including Glasgow Prognostic Score (GPS), systemic immune inflammation index (SII), modified Glasgow Prognostic Score (mGPS), prognostic index (PI), CRP-to-albumin ratio (CAR), lymphocyte-to-monocyte ratio (LMR), and lymphocyte-to-CRP ratio (LCR).[6] Different from IINS, most of prognostic biomarkers are different combination of two indexes from serum testing at present, which cannot reflect the immune and nutritive function of the body, in resulting inevitable biases and prediction inaccuracy.[19]

To our knowledge, this study is the first to suggest that pretreatment IINS might serve as a robust prognostic score in the treatment

TABLE 2 Relationship between IINS groups and response to anti-PD-1 treatment

Best Overall Response	No. of Patients (%)			
	Overall n = 101	IINS≤3 (n = 66)	IINS>3 (n = 35)	p value
CR	0 (0)	0 (0)	0 (0)	
PR	31 (30.7)	26 (83.9)	5 (16.1)	.017
SD	26 (25.7)	23 (88.5)	3 (11.5)	.008
PD	42 (41.6)	16 (38.1)	26 (61.9)	<.001
Objective response	31 (30.7)	26 (83.9)	5 (16.1)	.017
Disease control rate	57 (56.4)	49 (48.5)	8 (7.9)	<.001

Abbreviations: CR, complete response; PD, disease progression; PR, partial response; SD, stable disease.

TABLE 3 Univariate and multivariate time-dependent Cox regression analyses of the prognostic factors for OS

OS Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Child–Pugh grade				
A	1 [Ref.]			
B	1.029 (0.382–2.768)	.955	0.744 (0.210–2.630)	.646
C	5.051 (1.069–23.874)	.041	1.090 (0.036–33.223)	.961
BCLC Stage				
B	1 [Ref.]			
C	0.543 (0.153–1.931)	.345	0.529 (0.135–2.084)	.363
D	6.326 (1.664–24.051)	.007	2.861 (0.444–18.446)	.269
Tumor number (Single/Multiple)	3.755 (1.086–12.988)	.037	5.111 (1.075–24.299)	.04
Extrahepatic metastasis (no/yes)	0.609 (0.379–0.979)	.041	1.093 (0.318–3.760)	.888
CA19-9 (U/ml) (≤18.31:>18.31)	5.808 (1.911–17.652)	.002	2.546 (0.726–8.926)	.144
Cycles of anti-PD-1	0.863 (0.788–0.945)	.001	0.921 (0.827–1.025)	.131
Combined with target therapy (no/yes)	0.256 (0.098–0.666)	.005	0.344 (0.104–1.131)	.079
IINS				
High group (IINS≦3)	1 [Ref.]			
Low group (IINS>3)	5.858 (2.077–16.519)	.001	3.746 (1.049–13.379	.042

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CA19-9, carbohydrate antigen 19–9; HR, hazard ratio, CI confidence interval; IINS, inflammation-immunity-nutrition score; OS, overall survival; PD-1, programmed cell death protein 1.

of HCC patients with PD-1 inhibitors. Our results demonstrated that OS and PFS significantly improved in HCC patients who were treated with PD-1 inhibitors with a low IINS compared with those with a high IINS. IINS-CA19-9 classification may be highly effective for predicting the prognosis of HCC patients who were treated with PD-1 inhibitors. In addition, further comparison revealed that apart from Child–Pugh grade, AFP, NLR, and PLR, hsCRP/ALB, hsCRP/LYM, and PNI were also inferior to IINS in prognostic performance. Thus, IINS could be acknowledged as have better predictive ability than other inflammation-based prognostic scores.

Tumor-promoting inflammation is considered as one of the characteristics of cancer development,[20] several studies have demonstrated that inflammatory response is correlated with the efficacy of anti-PD-1 therapy in advanced types of cancer, including HCC.[21,22] Emerging evidence has shown that inflammation-based prognostic scores exhibited a promising discriminatory ability in predicting prognosis of HCC patients treated with PD-1 inhibitors.[5,6] HsCRP, LYM, and ALB are the major components of inflammation-based prognostic scores and were found to be closely correlated with inflammation, immunity, and nutrition, respectively.[23,24] Previous studies have also reported the prognostic values of hsCRP/LYM, hsCRP/ALB, and PNI for different types of cancer.[8,9,24,25] The underlying mechanism has not been well clarified. In our study, one possible explanation could be that interleukin (IL)-6, one of the main inducers of CRP production has been showed to promote tumor growth and metastasis.[26–28] In addition, in the tumor microenvironment, the depletion of lymphocytes, such as CD4- and CD8-positive T cells, would lead to disabling immune surveillance and killing.[29,30] A retrospective study indicated that nutrition and metabolism in patients with advanced HCC were closely associated with the efficiency of anti-PD-1 treatment and
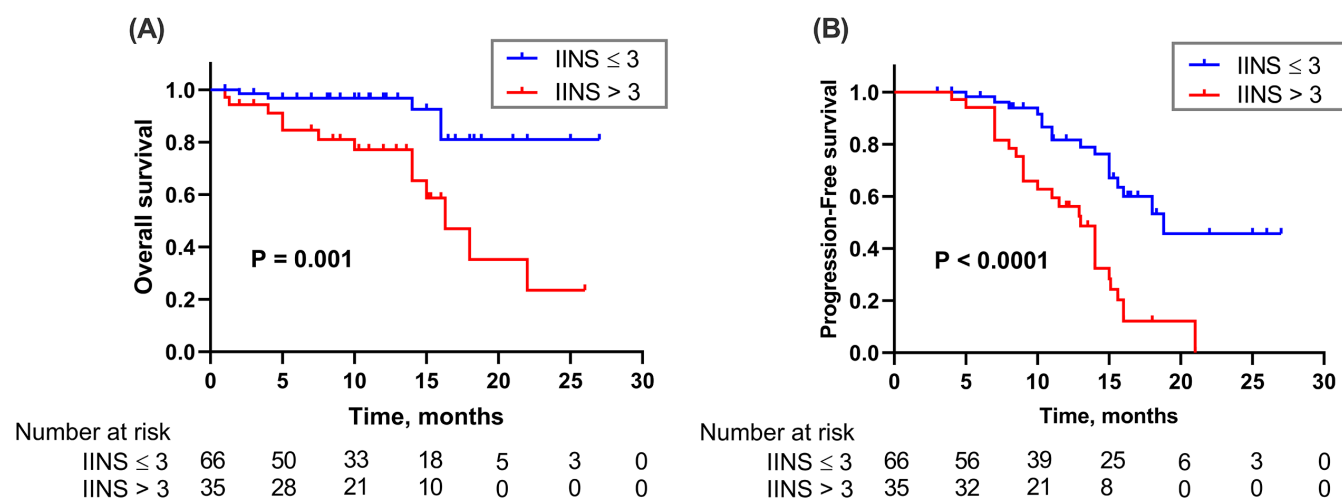

FIGURE 2 Kaplan–Meier curves of overall survival (A) and progression-free survival (B) according to inflammation-immunity-nutrition Score (IINS) groups

TABLE 4 Univariate and multivariate time-dependent Cox regression analyses of the prognostic factors for PFS

PFS	Univariate Analysis		Multivariate Analysis	
Characteristics	HR (95% CI)	p value	HR (95% CI)	p value
BCLC Stage (B/C/D)				
B	1 [Ref.]			
C	0.861 (0.427–1.735)	.675	0.708 (0.173–2.895)	.630
D	3.671 (1.239–10.873)	.019	2.358 (0.460–12.099)	.304
Extrahepatic metastasis (no/yes)	2.304 (1.261–4.209)	.007	1.481 (0.518–4.235)	.464
ALB (g/L) (≤35:<35)	0.514 (0.280–0.942)	.031	1.458 (0.401–5.308)	.567
CA199 (U/ml) (≤18.31:>18.31)	5.808 (1.911–17.652)	.002	2.470 (0.723–8.445)	.149
Cycles of anti-PD−1	0.918 (0.871–0.967)	.001	0.920 (0.828–1.023)	.122
Combined with target therapy (no/yes)	0.496 (0.270–0.913)	.024	0.329 (0.108–1.007)	.051
IINS				
Low group (IINS≤3)	1 [Ref.]			
High group (IINS>3)	3.909 (2.108–7.246)	<.0001	3.850 (1.007–14.727)	.049

Abbreviations: PFS, progression-free survival; HR, hazard ratio, CI confidence interval; BCLC, Barcelona Clinic Liver Cancer; ALB, albumin; CA19-9, carbohydrate antigen 19–9; PD-1, programmed cell death protein 1; IINS, inflammation-immunity-nutrition score.
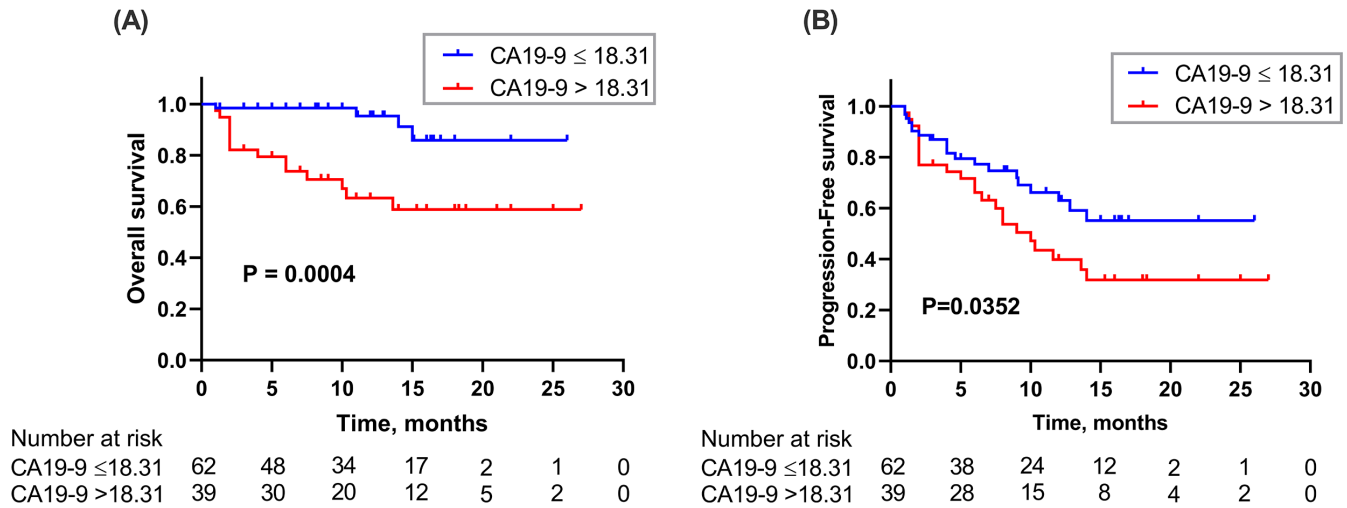
FIGURE 3 Kaplan–Meier curves were generated to analyze the overall survival (A) and progression-free survival (B) differences among 101 HCC patients treated with PD-1 inhibitors who were divided according to the cutoff value of the CA19-9
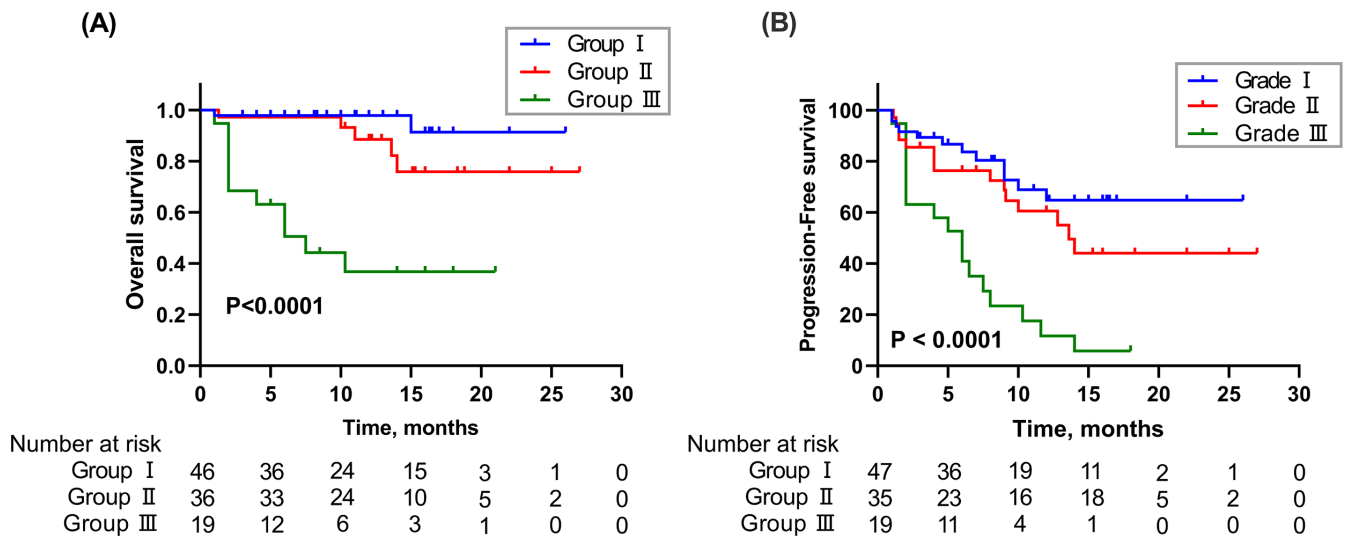

FIGURE 4 Kaplan–Meier survival curves for overall survival (A) and progression-free survival (B) according to IINS-CA19-9 classification
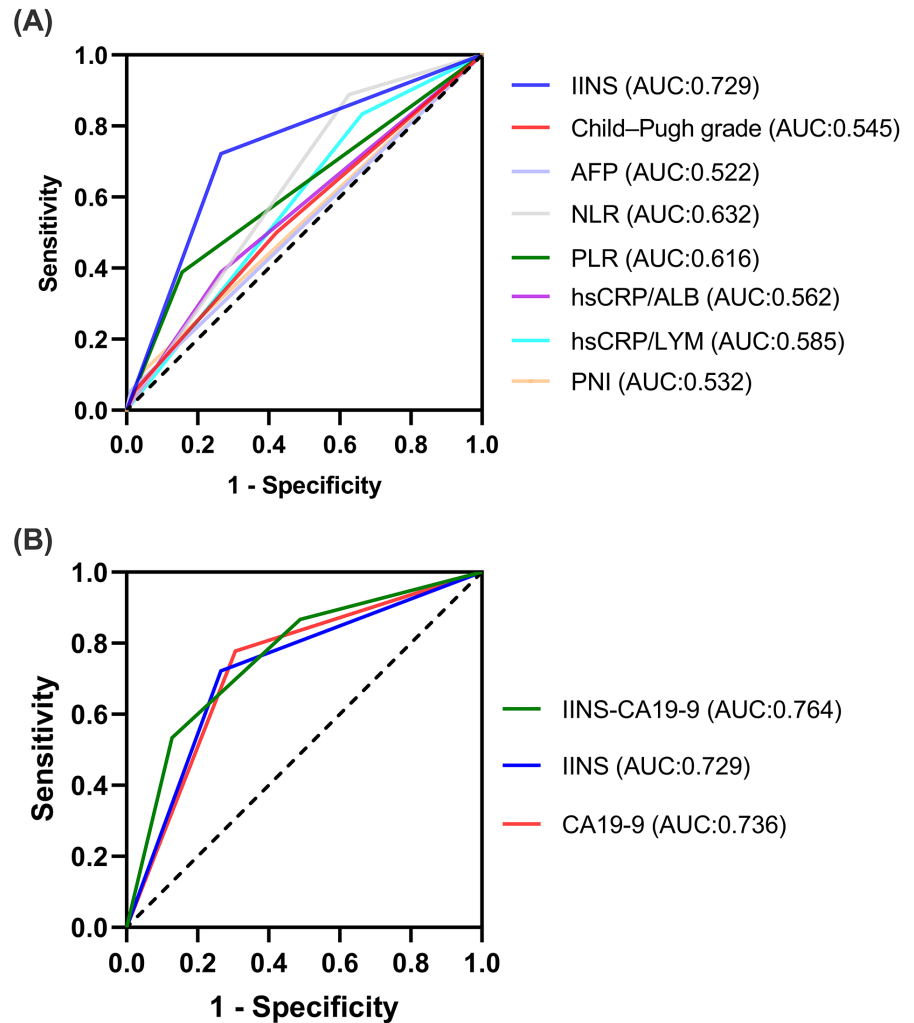
TABLE 5 Comparison of the prognostic performance between the indices in overall survival of HCC patients treated with PD-1 inhibitors

Variables	Calculations	Cut off value	AUC (95% CI)	Specificity	Sensitivity	p value
IINS			0.729 (0.597–0.861)	0.722	0.735	.002
CA19-9		18.31	0.736 (0.608–0.863)	0.693	0.778	.002
IINS-CA19-9			0.764 (0.631–0.897)	0.872	0.533	.001
Child–Pugh grade			0.545 (0.395–0.694)	0.578	0.500	.552
AFP		0.755	0.522 (0.370–0.673)	0.361	0.75	.773
NLR	Neutrophil count: lymphocyte count	2.79	0.632 (0.502–0.760)	0.373	0.889	.082
PLR	Platelet count: lymphocyte count	197.3	0.616 (0.463–0.770)	0.843	0.389	.124
hsCRP/ALB	hsCRP: ALB	0.7	0.562 (0.411–0.713)	0.735	0.389	.412
hsCRP/LYM	hsCRP: LYM	2.59	0.585 (0.448–0.723)	0.337	0.833	.258
PNI	ALB +LYM count ×5	50.63	0.532 (0.380–0.684)	0.952	0.111	.677

Abbreviations: IINS, inflammation-immunity-nutrition score; CA19-9, carbohydrate antigen 19–9; AFP, α-fetoprotein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; hsCRP, high-sensitivity C-reactive protein; LYM, lymphocyte; ALB, albumin; PNI, prognostic nutritional index.

FIGURE 5 Comparison of ROC curves for the outcome prediction between IINS and other traditional indicators (A), CA19-9 and IINS-CA19-9 scores (B) in HCC patients treated with anti-PD-1 therapy

(A)

IINS (AUC:0.729)
Child–Pugh grade (AUC:0.545)
AFP (AUC:0.522)
NLR (AUC:0.632)
PLR (AUC:0.616)
hsCRP/ALB (AUC:0.562)
hsCRP/LYM (AUC:0.585)
PNI (AUC:0.532)

(B)

IINS-CA19-9 (AUC:0.764)
IINS (AUC:0.729)
CA19-9 (AUC:0.736)

survival benefits, and ALB was positively correlated with efficacy.[31] Low serum ALB levels reflect a state of malnutrition, which would weaken cellular and humoral immunity, phagocytic activities, and other defensive systems in cancer patients.[32]

CA19-9 is a widely used biomarker for pancreatic, biliary, gastric, esophageal, and colonic cancers.[33] Some studies have shown that an elevated CA19-9 level was associated with poor prognosis of HCC patients who underwent resection or hepatic transplantation.[34,35] Furthermore, a prospective study reported that CA19-9 served as an independent predictor for HCC patients' survival.[36] CA19-9 level mainly reflects the pathological conditions, while IINS indicates a patient's overall status, including inflammation, immune, and nutritional status.

In clinical practice, this study suggested that inflammation, immune, and nutritional status in patients with HCC were closely related to anti-PD-1 immunotherapy efficacy and survival benefit, clearly imply the presence of a chance for enhanced clinical outcomes or even cure for those HCC patients presenting with lower systemic inflammation loads and favorable immunonutritional status. Hence, reducing levels of systemic inflammation, improving immunity, and nutrition support may be the feasible strategies to enhance treatment efficacy and survival in those patients with high IINS. Furthermore, based on the combined application of IINS

and CA19-9, individualized prediction of prognosis was performed, in which a good response to anti-PD-1 therapy could be achieved in group I, followed by moderate and poor responses in groups II and III, respectively. For patients with elevated values of IINS and CA19-9 (group III), considering the reduced prognostic benefit, it is essential to indicate the possibility of combination with targeted therapy or an early change in therapy. For patients without elevated values of IINS or CA19-9 (group I), the surgeon should make patients with unresectable HCC achieve down-staging or radical resection, thereby improving patients' survival as long as possible.

This study also has certain limitations. First, our research uses a retrospective design. Second, it is a single-center study with a relatively short median follow-up (11.1 months). Third, patients received non-single PD-1 inhibitors during the treatment, which inevitably caused bias. In addition, the sample size we studied is relatively small. Further multicenter, larger-scale prospective research is needed to validate our findings.

5 | CONCLUSION

Our results suggest that inflammation-immunity-nutrition score (IINS) may present as an independent prognostic factor for patients

with HCC treated with anti-PD-1 therapy. Specifically, pretreatment IINS-CA19-9 scores are better than the IINS alone in predicting the prognosis of HCC patients treated with anti-PD-1 therapy. A low IINS-CA19-9 score (group I, good) suggests that maintenance therapy and close follow-up should be considered. Identifying patients who may have poor short-term outcomes can help optimize their treatment strategies, such as combining PD-1 inhibitors with target therapy or other treatments.

AUTHOR CONTRIBUTIONS

Z Zhang was responsible for study conception and design, data acquisition, data analysis, and drafting and revision of the manuscript. X Huang was responsible for study conception and design, data analysis and drafting, and revision of the manuscript. D Zhong, Z Dai, J Shang, Y Yao, T Feng, H Zou, and C Lai were responsible for data acquisition. Y Liang was responsible for data analysis and drafting and revision of the manuscript.

ETHICAL APPROVAL

This study was approved by the Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital ethics committee (NO2021-447). Informed consent was obtained from all patients and subjects.

DATA AVAIL ABILIT Y STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

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