

# Inflammation-Based Scores Predict Responses to PD-1 Inhibitor Treatment in Intrahepatic Cholangiocarcinoma

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**Purpose:** Inflammatory response is related to tumor progression and patient survival. We aimed to clarify the prognostic value of the inflammation-based scores in intrahepatic cholangiocarcinoma (ICC) patients receiving anti-PD1 therapy.

**Patients and Methods:** A total of 73 patients who received anti-PD-1 therapy from February 2019 to February 2021 were included in the study. Representative inflammation-based prognostic scores, including C-reactive protein (CRP), the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-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), and prognostic index (PI), were assessed for prediction accuracy using Kaplan–Meier survival curves and time-dependent receiver operating characteristic (ROC). All the ten inflammation-based prognostic scores were measured before receiving anti-PD1 therapy.

**Results:** All the ten inflammation-based prognostic scores showed good discriminatory ability in terms of overall survival (OS) (all  $P < 0.01$ ), the higher the score, the worse the prognosis, while the CRP score was a remarkable independent predictor for OS in multivariate analysis (hazard ratio, 6.032; confidence interval, 2.467–14.752;  $P < 0.001$ ). The area under the ROC curve at 6 months, 12 months, 18 months and 24 months consistently demonstrated that the predictive value of the CRP score was superior to other inflammation-based scores.

**Conclusion:** Inflammation-based scores predict the efficacy of anti-PD-1 therapy in patients with ICC and CRP score superior to the other inflammation-based prognostic scores in terms of predictive ability.

**Keywords:** inflammation-based score, intrahepatic cholangiocarcinoma, anti-PD-1 treatment, overall survival, C-reactive protein

## Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy with a high degree of malignancy and poor prognosis.<sup>1,2</sup> The global incidence of ICC is expected to increase ten-fold over the next 20 to 30 years.<sup>3</sup> However, the treatment modalities of ICC are still limited. Most patients are diagnosed at advanced stages, when the available systemic therapies are of limited benefit.<sup>4</sup> In recent years, research on programmed cell death protein-1 (PD-1) inhibitors has continued to emerge,<sup>5</sup> showing promising effects on patients with ICC. However, the efficacy of immunotherapy varies from person to person, based on results from completed studies of anti-PD1 monotherapy in ICC, objective response rates (ORRs) ranged from 3% to 21.4%.<sup>6,7</sup> Meanwhile, the incidence of treatment-related adverse events was more than 90%, the most common all-grade adverse events were anaemia, fatigue, and dysphagia, respectively, and the most common grade 3 or higher adverse events were neutropenia, hypertension, lipase increased, and lymphopenia.<sup>8</sup> Practical and

reliable prognostic predictors are needed which can differentiate the ICC patients with the highest potential to benefit from PD-1 inhibitors. Also, this would help avoid unnecessary therapy and the occurrence of adverse events.

Cancer-related inflammation is recognized as a hallmark of cancer.<sup>9</sup> In established cancers, there is increasing evidence for the roles that local immune response and systemic inflammation have in progression of tumors and survival of patients with cancer.<sup>10,11</sup> For the past few years, many inflammation-based prognostic scores composed of systemic inflammatory response factors were proposed to exhibit good predictive ability in cancer prognosis, which included C-reactive protein (CRP),<sup>12,13</sup> platelet-to-lymphocyte ratio (PLR),<sup>14</sup> neutrophil-to-lymphocyte ratio (NLR),<sup>15,16</sup> lymphocyte-to-CRP ratio (LCR),<sup>17,18</sup> lymphocyte-to-monocyte ratio (LMR),<sup>19,20</sup> (SII),<sup>21,22</sup> CRP-to-albumin (ALB) ratio (CAR),<sup>23,24</sup> prognostic nutritional index (PNI),<sup>25,26</sup> Glasgow Prognostic Score (GPS),<sup>27,28</sup> and prognostic Index (PI).<sup>29</sup> These inflammation-based scores have been reported to be associated with the value in predicting survival after anti-PD-1 treatment in HCC patients.<sup>30</sup> However, the function in predicting survival in ICC patients who received PD-1 inhibitors has not been clarified ever.

Herein, we aimed to evaluate the prognostic role of these inflammation-based scores and carry a direct comparison of various inflammation-based scores in ICC patients after anti-PD1 treatment.

## Materials and Methods

### Patients

A total of 73 patients diagnosed with ICC who received anti-PD-1 therapy between February 2019 and February 2021 at the Sun Yat-sen University Cancer Center were selected as the study population. Patients were included based on the following criteria: (a) aged from 18 to 75 years; (b) histological confirmation of ICC; (c) had confirmed records of receiving PD-1 inhibitors; (d) had a performance status (PS) score less than 2; (e) had no other malignant tumors; and (f) had complete medical and low-up data. The study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment.

### Treatment Procedure

PD-1 inhibitors were all administered according to the following regimens: Nivolumab at 1–3 mg/kg body weight per 2 weeks, Pembrolizumab at 200mg per 3 weeks, Toripalimab, Camrelizumab and Sintilimab at 240 mg, 200mg and 200mg per 2 weeks. PD-1 inhibitors could be combined with locoregional interventional therapies or tyrosine kinase inhibitors (TKIs) including sorafenib, lenvatinib or apatinib during treatment ([Table S1](#)).

### Data Collection

The demographic and clinical characteristics included age, gender, hepatitis, ALT (U/L), AST (U/L), ALB (g/L), TBIL (umol/L), CA19-9 (U/mL), largest tumor size (cm), tumor number, macroscopic vascular invasion, lymph node metastasis, combination therapy, TNM stage, CRP, PLR, NLR, LCR, LMR, SII, CAR, PNI, GPS, PI. Demographic and clinical characteristics are summarized in [Table 1](#).

The counts of white blood cells, neutrophils, lymphocytes, monocytes, and platelets and the levels of CRP and ALB were measured within a period of 5 days prior to the onset of receiving anti-PD1 therapy. Serum samples were collected and clotted at room temperature, then centrifuged at 3500r/min for 10 min, which could be used to estimate the level of serum biomarkers. The concentrations of albumin and total proteins were measured using a Roche Cobas 702 Automatic Biochemical Analyzer. Albumin and total proteins were measured using colorimetry. The levels of neutrophil, lymphocyte, and platelet were derived from the blood count using a Sysmex XN-2000 automatic blood-cell counter. The coefficient of variation of the two tests in our laboratory is  $\leq 5\%$ . Radiological response was evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) performed at a baseline, 6–12 weeks after treatment initiation, and approximately every 3 months thereafter according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The CRP, PLR, NLR, LCR, LMR, SII, CAR, GPS, PI and PNI were calculated as described in [Table 2](#). Overall survival (OS) was defined as the time interval from anti-PD-1 initiation to cancer-related death.

**Table I** Baseline Characteristics of the Enrolled Patients

Variables	N = 73
Age, y	57 (31–75)
Gender (male/female)	49/24 (67.1/32.9)
Hepatitis (yes /no)	36/37 (49.3/50.7)
ALT, U/L, (>/≤50)	27.6 (6.5–133.8)
AST, U/L, (>/≤40)	35.1 (14.5–207.7)
ALB, g/L, (>/≤35)	41.7 (25.9–50.1)
TBIL, umol/L, (>/≤17.1)	11.2 (2.6–45.3)
CA19-9U/mL, (>/≤100)	61.6 (1.2–35,704)
Largest tumour size, cm	8.2 (3.6–17.2)
Tumor number (>1/1)	50/23 (68.5/31.5)
Macrovascular invasion (yes/no)	33/40 (45.2/54.8)
Lymph node metastasis (yes/no)	48/25 (65.8/34.2)
TNM stage (III–IV /II)	50/23 (68.5/31.6)
CRP (1/0)	38/35 (52.4/47.9)
PLR (1/0)	18/55 (24.7/75.3)
NLR (1/0)	37/36 (50.7/49.3)
LCR (1/0)	40/33 (54.8/45.2)
LMR (1/0)	22/51 (30.1/69.9)
SII (1/0)	24/49 (32.9/67.1)
CAR (1/0)	39/34 (53.4/46.6)
PNI (1/0)	36/37 (49.3/50.7)
GPS (2/1/0)	7/40/26 (9.6/54.8/35.6)
PI (2/1/0)	12/38/23 (16.4/52.1/31.5)

**Note:** Values are presented as the median (range) or n (%).

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; TNM, tumour-node-metastasis; CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; PI, prognostic index.

## Statistical Analysis

The results were described to use the median and range for nonnormally distributed values. Groups were compared by using Student's *t*-test for continuous data and the  $\chi^2$  test for categorical data. Independent predictive variables were determined with univariate and multivariate Cox regression analysis for OS by the method of Forward LR. The risk stratification survival curves were represented by Kaplan–Meier curves and analyzed using 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 R version 4.0.2 for CRP, PLR, NLR, LCR, LMR, SII, CAR, and PNI ([Supplemental Figure 1A–H](#)). For composite indicators, the GPS and PI scores were calculated as generally reported.<sup>28,29</sup> 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. All data analyses were performed using SPSS 25.0 software (SPSS Inc., Chicago, IL) and R version 4.0.2.

## Results

### Patient Characteristics

A total of 73 patients with advanced ICC were treated with anti-PD-1 at the Sun Yat-sen University Cancer Center were included in the study. The cohort includes 49 (67.1%) males and 24 (32.9%) females. Ages ranged from 31 to 75 years with a median of 57 years. A majority of patients had multiple tumors (68.5%). A total of 33 (45.2%) patients had macrovascular invasion, and 48 (65.8%) patients had lymph node metastasis. The range of tumor size is from 3.6 to

**Table 2** Systemic Inflammation-Based Prognostic Scores

Scoring System	Score
C-reactive protein (CRP) CRP ≤ 12.75 CRP > 12.75	0 1
Platelet-to-lymphocyte ratio (PLR) Platelet count (×10 <sup>9</sup> /L): lymphocyte count (×10 <sup>9</sup> /L) ≤ 222.52 Platelet count (×10 <sup>9</sup> /L): lymphocyte count (×10 <sup>9</sup> /L) > 222.52	0 1
Neutrophil-to-lymphocyte ratio (NLR) Neutrophil count (×10 <sup>9</sup> /L): lymphocyte count (×10 <sup>9</sup> /L) ≤ 3.56 Neutrophil count (×10 <sup>9</sup> /L): lymphocyte count (×10 <sup>9</sup> /L) > 3.56	0 1
Lymphocyte-to-C-reactive protein ratio (LCR) 10 <sup>4</sup> × lymphocyte count (×10 <sup>9</sup> /L): CRP (mg/L) > 1166.91 10 <sup>4</sup> × lymphocyte count (×10 <sup>9</sup> /L): CRP (mg/L) ≤ 1166.91	0 1
Lymphocyte-to-monocyte ratio (LMR) Lymphocyte count (×10 <sup>9</sup> /L): monocyte count (×10 <sup>9</sup> /L) ≤ 2.15 Lymphocyte count (×10 <sup>9</sup> /L): monocyte count (×10 <sup>9</sup> /L) > 2.15	0 1
Systemic Immune-inflammation Index (SII) Platelet count (×10 <sup>9</sup> /L) × neutrophil count (×10 <sup>9</sup> /L)/lymphocyte count (×10 <sup>9</sup> /L) ≤ 1271.81 Platelet count (×10 <sup>9</sup> /L) × neutrophil count (×10 <sup>9</sup> /L)/lymphocyte count (×10 <sup>9</sup> /L) > 1271.81	0 1
CRP-to-albumin ratio (CAR) CRP (mg/L): albumin (g/L) ≤ 0.3 CRP (mg/L): albumin (g/L) > 0.3	0 1
Glasgow Prognostic Score (GPS) CRP ≤ 10 mg/L and albumin ≥ 35 g/L CRP ≤ 10 mg/L and albumin < 35 g/L CRP > 10 mg/L and albumin ≥ 35 g/L CRP > 10 mg/L and albumin < 35 g/L	0 1 1 2
Prognostic Index (PI) CRP ≤ 10 mg/L and WBC count ≤ 10 × 10 <sup>9</sup> /L CRP ≤ 10 mg/L and WBC count > 10 × 10 <sup>9</sup> /L CRP > 10 mg/L and WBC count ≤ 10 × 10 <sup>9</sup> /L CRP > 10 mg/L and WBC count > 10 × 10 <sup>9</sup> /L	0 1 1 2
Prognostic Nutritional Index (PNI) Albumin (g/L) + 5 × lymphocyte count (×10 <sup>9</sup> /L) > 49 Albumin (g/L) + 5 × lymphocyte count (×10 <sup>9</sup> /L) ≤ 49	0 1

**Abbreviation:** WBC, white blood cell.

21.5 cm, with a median of 8.2 cm. The clinical characteristics, including the ten inflammation-based scores of the patients, are summarized in [Table 1](#). The average follow-up time after immunotherapy was 11.2 months. The median OS time was 10.5 months (95% CI: 8.9–12.1 months).

## Univariate and Multivariate Cox Regression Analyses in the Cohorts

Univariate analysis involved prognostic factors related to ethnic characteristics, liver function, tumor burden and the ten inflammation-based scores. All ten inflammation scores were identified as significant prognostic factors for OS in addition to liver function and tumor burden. The details are described in [Table 3](#). The multivariate Cox proportional

**Table 3** Univariate and Multivariate Cox Regression Analyses of Risk Factors for Overall Survival

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age, y ( $\leq$ / $>$ 50)	0.418	0.220–0.795	0.008			
Gender (male/female)	1.287	0.648–2.554	0.471			
Hepatitis (yes /no)	1.217	0.649–2.283	0.541			
ALT, U/L, ( $>$ / $\leq$ 50)	2.090	0.969–4.507	0.060			
AST, U/L, ( $>$ / $\leq$ 40)	1.289	0.689–2.413	0.427			
ALB, g/L, ( $>$ / $\leq$ 35)	0.417	0.171–1.015	0.054			
TBIL, umol/L, ( $>$ / $\leq$ 17.1)	1.379	0.601–3.163	0.448			
CA19-9U/mL, ( $>$ / $\leq$ 100)	1.426	0.762–2.668	0.268			
Largest tumour size ( $>$ / $\leq$ 10 cm)	1.15	0.615–2.152	0.662			
Tumor number ( $>$ 1/1)	1.546	0.783–3.053	0.209			
Macrovascular invasion (yes/no)	1.233	0.661–2.300	0.509			
Lymph node metastasis (yes/no)	3.316	1.521–7.229	0.003	3.112	1.372–7.056	0.007
TNM stage (III–IV /II)	3.311	1.460–7.510	0.004			
CRP (1/0)	8.405	3.549–19.906	<0.001	6.032	2.467–14.752	<0.001
PLR (1/0)	3.618	1.772–7.387	<0.001	2.433	1.151–5.145	0.020
NLR (1/0)	2.530	1.324–4.838	0.005			
LCR (1/0)	5.695	2.622–12.368	<0.001			
LMR (1/0)	2.336	1.209–4.512	0.012			
SII (1/0)	3.751	1.895–7.426	<0.001			
CAR (1/0)	6.731	2.968–15.265	<0.001			
PNI (1/0)	3.777	1.834–7.779	<0.001			
GPS						
0	Reference	Reference	Reference			
1	3.564	1.625–7.815	0.002			
2	6.350	2.009–20.069	0.002			
PI						
0	Reference	Reference	Reference			
1	4.485	1.817–11.070	0.001			
2	9.148	3.072–27.238	<0.001			

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

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; TNM, tumour-node-metastasis; CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; PI, prognostic index.

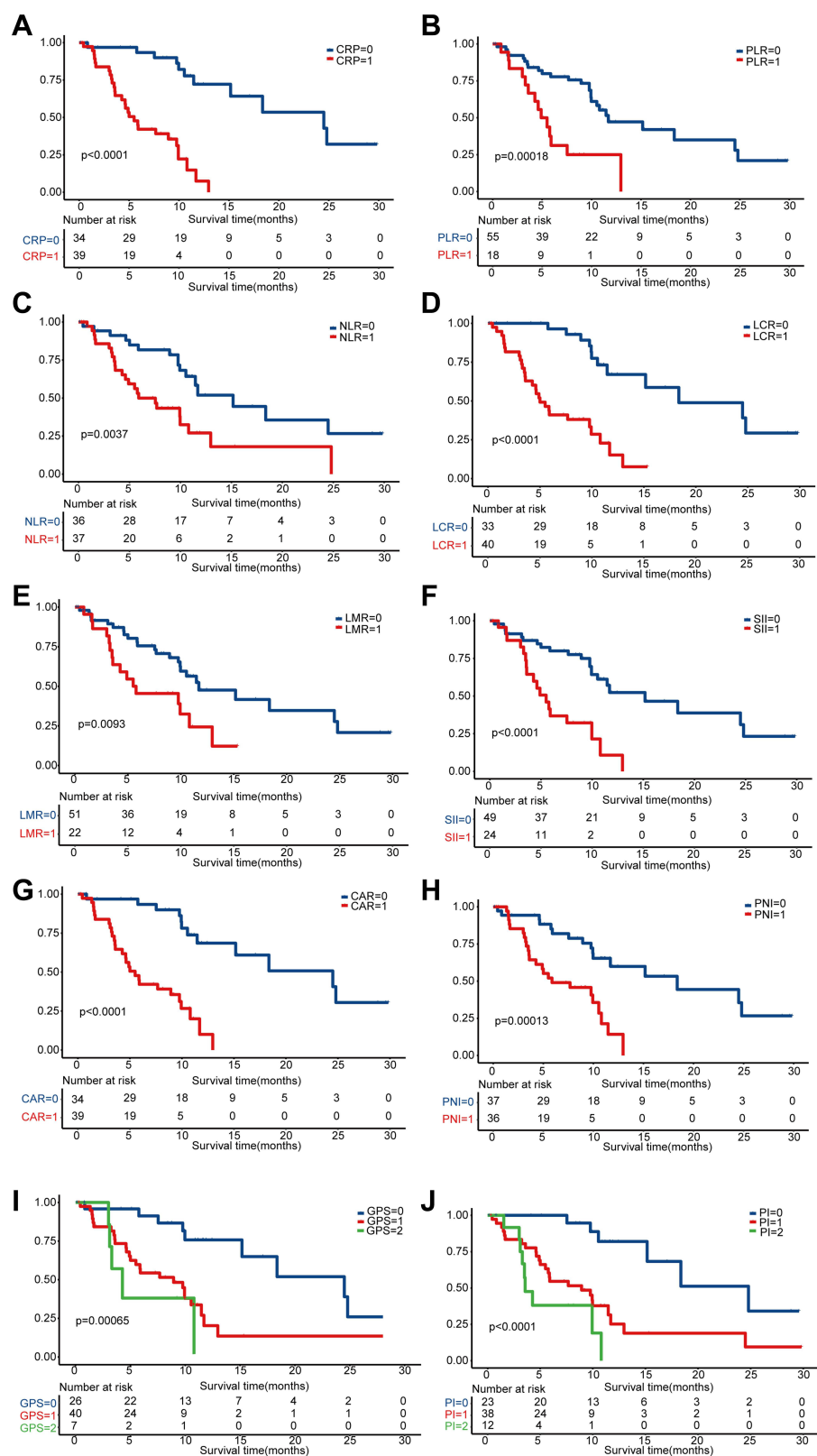
analysis revealed that elevated serum CRP ( $P < 0.001$ ), lymph node metastasis ( $P = 0.007$ ), and PLR ( $P = 0.02$ ) were significant and independent prognostic factors of OS (Table 3).

## Overall Survival

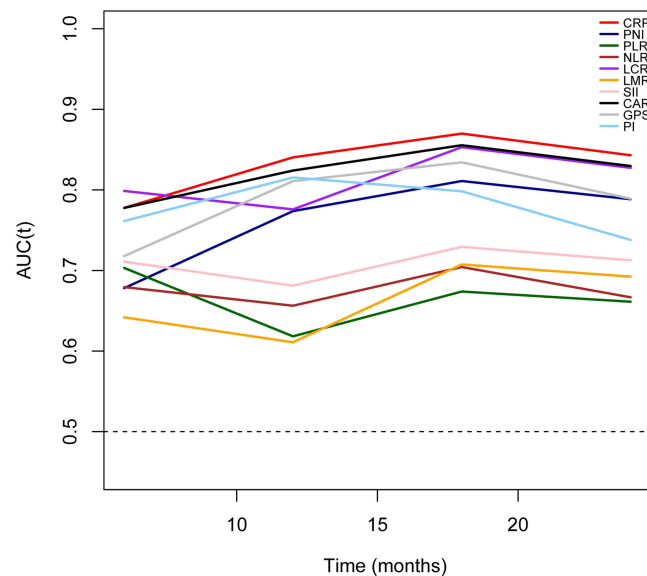
All inflammation-based scores were associated with the OS of patients who received PD1 inhibitors (Figure 1). Low CRP PLR, NLR, LCR, LMR, SII, CAR, GPS, PI and PNI scores indicated good prognosis (all  $P < 0.01$ ). The CRP score and PLR score remained as significant and independent predictors of OS in multivariate analysis. The CRP score differentiated the ICC patients into two groups with distinct prognoses. The median OS time was 20.4 months, 6.5 months.

## 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 (Supplemental Figure 2A–D), and the CRP score was better than the others. The AUC of the time-dependent ROC curve showed that the CRP score had a better ability to predict OS. Plots of the time-dependent



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



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

AUC are shown in Figure 2. The area under the receiver operating characteristic curve (AUROC) was calculated, and the values are provided in Table 4. The CRP scores consistently had higher values than the other inflammation-based scores.

## Relationships Between the CRP Score and Clinical Characteristics and Efficacy

The correlations between the CRP score and clinical characteristics are shown in Table 5. A high CRP score is associated with lower albumin ( $P < 0.001$ ), lymph node metastasis ( $P = 0.048$ ), and worse TNM stage ( $P = 0.045$ ). The survival curves of patients are stratified according to the presence of lymph node metastasis and TNM stage (Supplemental Figure 3A–D). Tumor response analysis indicated that the objective response rate (ORR) (22.9% vs 5.3%,  $P = 0.023$ ) and disease control rate (DCR) (77.1% vs 52.6%,  $P = 0.002$ ) were higher in the low CRP group.

**Table 4** AUROC for the Comparison of Different Inflammatory-Based Scores

Scores	6-Month AUROC	12-Month AUROC	18-Month AUROC	24-Month AUROC
CRP	0.778(68.42–87.11)	0.84(72.65–95.42)	0.87(79.01–94.96)	0.843(75.64–92.96)
PLR	0.703(58.92–81.71)	0.618(50.38–73.29)	0.674(59.36–75.42)	0.661(58.38–73.88)
NLR	0.679(56.27–79.61)	0.656(49.85–81.41)	0.704(53.13–87.73)	0.667(47.01–86.34)
LCR	0.799(71.37–88.38)	0.776(63.67–91.49)	0.853(77.12–93.48)	0.827(74.03–91.45)
LMR	0.642(52.04–76.35)	0.611(46.94–75.24)	0.707(62.32–79.17)	0.692(61.00–77.47)
SII	0.711(59.45–82.76)	0.681(56.10–80.12)	0.729(64.42–81.45)	0.713(62.88–79.65)
CAR	0.778(68.42–87.11)	0.824(70.83–93.98)	0.855(77.40–93.69)	0.83(74.26–91.67)
GPS	0.718(61.30–82.28)	0.811(68.02–94.15)	0.834(68.35–98.50)	0.789(61.06–96.77)
PI	0.761(66.73–85.55)	0.815(69.10–93.99)	0.798(63.15–96.51)	0.738(64.46–89.67)
PNI	0.678(56.10–79.52)	0.774(65.41–89.33)	0.811(72.63–89.58)	0.788(70.10–87.59)

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

**Abbreviations:** AUROC, area under the receiver operating characteristic curve; CRP, C-reactive protein; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; CAR, C-reactive protein-to-albumin ratio; PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; PI, prognostic index.



**Table 5** Baseline Characteristics of the Patients Grouped by CRP Score

Variables	CRP≤12.75	CRP>12.75	P
	N=35	N=38	
Age, y	57 (36–77)	56.5 (31–76)	0.629
Gender (male/female)	19/16 (54.3/45.7)	30/8 (78.9/21.1)	0.025
Hepatitis (yes /no)	18/17 (51.4/48.6)	18/20 (50/45.9)	0.729
ALT, U/L, (>/≤50)	25.7 (6.7–133.8)	28.5 (6.5–95.4)	0.834
AST, U/L, (>/≤40)	35 (14.5–207.7)	35.85 (17.6–168.6)	0.604
ALB, g/L, (>/≤35)	44.5 (33.4–50.1)	39.05 (25.9–47.1)	<0.001
TBIL, umol/L, (>/≤17.1)	12.6 (2.6–45.3)	10.85 (4.4–44.4)	0.711
CA19-9U/mL, (>/≤100)	40.15 (1.2–35,704)	217.75(1.54–9475)	0.068
Largest tumour size, cm	8.1 (3.6–17.2)	8.6 (5.5–15.8)	0.32
Tumor number (>1/1)	24/11 (68.6/31.4)	26/12 (68.4/31.6)	0.989
Macrovascular invasion (yes/no)	18/17 (51.4/48.6)	15/23 (39.5/60.5)	0.305
Lymph node metastasis (yes/no)	19/16 (54.3/45.7)	48/25 (65.8/34.2)	0.048
TNM stage (III–IV /II)	20/15 (57.1/42.9)	30/8 (78.9/21.1)	0.045
Best tumor response			
CR	0(0)	0(0)	
PR	8(22.9)	2(5.3)	
SD	19(54.3)	18(47.4)	
PD	8(22.9)	18(47.4)	
ORR	8(22.9)	2(5.3)	0.023
DCR	27(77.1)	20(52.6)	0.002

**Notes:** Values are presented as the median (range) or n (%). P-value < 0.05 is statistically significant.

**Abbreviations:** CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; TNM, tumour-node-metastasis; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

## Discussion

It is widely acknowledged that advanced ICC remains resistant to systemic treatments and therapy remains palliative. In recent years, immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1 (PD-1) checkpoints have demonstrated the potential for relatively tumor-specific immune disinhibition across a range of tumor types. Immune checkpoint inhibitor (ICB), especially PD-1 inhibitors, has been demonstrated in several studies to have a definite effect on patients with ICC. However, due to different biological specificities of ICC, even patients have different prognoses for the same anti-PD1 treatment. Prognostic indicators for the use of PD-1 inhibitors are urgently needed. Emerging evidence shows that inflammation-based scores are associated with cancer-specific survival, but what components of the systemic inflammatory response best predict survival in ICC patients within anti-PD1 treatment remains unclear. This study is the first to comprehensively identify that inflammation scoring systems are associated with the OS of ICC patients who received PD-1 inhibitor therapy. Moreover, the CRP score was found to be superior to the other inflammation-based scores in predicting survival.

ICC is associated with primary sclerosing cholangitis, primary biliary cirrhosis and other diseases that cause biliary tract inflammation and fibrosis.<sup>31</sup> Inflammation is crucial in the occurrence and development of ICC. Increasing evidence has shown that the inflammatory response is associated with the efficacy of PD-1 inhibitors in advanced cancers. The liver maintains a chronic state of immune tolerance that may be exploited by liver tumors, which further induce T cell exhaustion by upregulating immune checkpoints including TIM3, LAG3, PD-1, and CTLA-4,<sup>32,33</sup> suggesting that ICIs such as PD-1 inhibitors could potentially restore antitumor immunity in liver tumors.

As an acute inflammatory response biomarker, serum CRP has been recognized as an indicator of progression for several cancers. CRP refers to acute proteins induced by IL-6, produced in the liver, which rises sharply in plasma when the body is infected or tissue damaged.<sup>34</sup> CRP can activate complement and strengthen the phagocytosis of phagocytes



to play an opsonizing role, thereby removing pathogenic microorganisms and damaged, necrotic, and apoptotic tissue cells that invade the body, and plays an important protective role in the body's innate immune process.<sup>35,36</sup> Our study demonstrated that compared with other inflammation-based scores, the presence of a systemic inflammatory response revealed by CRP is the best tool to assess survival in ICC patients receiving PD-1 inhibitor therapy. CRP is an acute-phase protein and a well-accepted marker of cancer-induced systemic inflammation, a condition which is clinically often reflected in cancer symptoms such as weight loss, fatigue, and anorexia.<sup>37–39</sup> Therefore, the CRP level links with the clinical manifestations and may associate with the clinicopathological features of patients. The CRP level has been verified to be an effective prognostic predictor in many types of digestive system cancers, including ICC.<sup>17</sup> The underlying mechanism has not been well elucidated. In our study, one possible explanation is that elevated CRP indicates sustained inflammation that may reflect a pro-angiogenic tumour microenvironment. Also, it has been reported that elevated CRP can help identify patients with impaired T lymphocytes, leading to poor prognosis in malignancy.<sup>40</sup> On the other hand, CRP is associated with tumor immunosuppression. A previous study indicates that CRP can suppress proliferation and effector functions of activated CD4+ and CD8+ T cells from patients with melanoma.<sup>41</sup> Thus, elevated CRP may play important roles in the poor prognosis observed for ICC patients with anti-PD-1 treatment.

This study has several limitations. Firstly, this was a retrospective study conducted on a single-center cohort in China. Secondly, the molecular mechanisms underlying inflammation and ICC are unknown and further basic research is needed. Thirdly, most of patients in this cohort received combination treatment and confounding factors were inevitable. As we can know, the ORR of anti-PD1 monotherapy for primary liver cancer is too low, combination therapy may be the mainstream treatment, we cannot change the clinical treatment strategy. Consequently, it is necessary to conduct more bench-scale study to figure out intrinsic mechanism that can guide the anti-PD1 treatment. Finally, CRP is a sensitive acute-phase protein, which could be affected by many factors, such as acute and chronic inflammation, undocumented infection, and trauma. Therefore, serum CRP levels should be detected in the stable phase to avoid the interference of other potential factors.

In conclusion, this study had demonstrated that CRP score predicts anti-PD-1 therapy response and survival in the cohort including a total of 73 patients with ICC. Meanwhile, CRP score is superior to the other inflammation-based prognostic scores in terms of predictive ability. This is easy to use for risk stratification and help patients receive appropriate treatment.

## Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## Ethics Approval and Informed Consent

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 (Approval Number: B2020-250-01). The study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment.

## 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.

## Funding

This work is funded by the National Natural Science Foundation of China (No: 81874070).

## Disclosure

The authors declare that they have no conflicts of interest in this work.

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