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ORIGINAL RESEARCH

Prognostic Value of the SII-PNI Score in Unresectable HCC Treated with Transcatheter Arterial Chemoembolization Combined with Lenvatinib and PD-1 Inhibitors

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Purpose: The combined systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) (SII-PNI score) serves as a prognostic predictor in various malignancies. This study evaluates the prognostic value of the SII-PNI score in patients with unresectable hepatocellular carcinoma (uHCC) treated with transcatheter arterial chemoembolization combined with lenvatinib and PD-1 inhibitors (triple therapy).

Patients and Methods: This retrospective multicenter study included patients with uHCC treated with triple therapy from eight hospitals. The optimal cut-off values for SII and PNI were determined using X-tile. The SII-PNI score was categorized as follows: score of 0, low SII (≤cut-off value) and high PNI (>cut-off value); score of 1, either high SII-high PNI or low SII-low PNI; score of 2, high SII and low PNI. Survival curves were estimated and compared using the Kaplan–Meier method with the Log rank test.

Results: A total of 290 patients were included. The optimal cut-off values were 525.9 for SII and 44.0 for PNI. Patients were classified as SII-PNI score of 0 (n = 105), score of 1 (n = 124), and score of 2 (n = 61). Lower SII-PNI score was associated with better median overall survival (score of 0: not reached vs score of 1: 28.0 months vs score of 2: 19.7 months; $p < 0.001$). Similarly, the median progression-free survival for SII-PNI scores of 0, 1, and 2 was 25.5, 16.6, and 12.9 months, respectively ($p < 0.001$). Lower SII-PNI score also indicated better objective response rate ($p = 0.007$) and disease control rate ($p = 0.003$). The SII-PNI score was identified as an independent predictor of overall survival and progression-free survival in multivariate COX regression analysis.

Conclusion: The SII-PNI score is associated with survival and tumor response in patients with uHCC treated with triple therapy. This score aids in optimizing clinical decision-making for uHCC.

Keywords: hepatocellular carcinoma, immunity, inflammation, nutrition, prognosis, tumor response

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer globally, with the third highest mortality rate.[1] Although early-stage HCC can be potentially curable through surgery, most patients are diagnosed with unresectable HCC (uHCC).[2–4] Significant advancements have been made in therapeutic strategies for uHCC over the past decade, ranging from locoregional and systemic treatments.[5,6] Locoregional treatments combined with systemic agents may

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provide synergistic effects, enhancing antitumor activity.[6–8] In this context, the combination of transcatheter arterial chemoembolization (TACE), lenvatinib, and PD-1 inhibitors (triple therapy) has emerged as a promising treatment modality for uHCC.[9–14] However, due to tumor heterogeneity, the tumor response and survival outcomes vary significantly, with reported objective response rate (ORR) ranging from 26% to 87.2% and median overall survival (OS) ranging from 15.7 to 29 months.[14] Therefore, easily accessible, reliable, and practical prognostic factors are warranted to help optimize treatment strategies for these patients.

Given the important roles of inflammatory responses in tumorigenesis, progression, and metastasis, inflammation-based indexes have garnered attention as prognostic factors in various malignancies.[15,16] The systemic immune-inflammation index (SII), derived from lymphocyte, neutrophil, and platelet counts, was reported to be associated with therapeutic response and survival in multiple tumors.[17] Yao et al demonstrated that changes in SII were correlated with outcomes in patients with hepatitis B-related HCC treated with lenvatinib and PD-1 inhibitors.[18] Additionally, evidence suggests that nutritional status correlates with treatment tolerability, tumor progression, and patient prognosis.[19,20] The prognostic nutritional index (PNI), which encompasses serum albumin levels and lymphocyte counts, has been identified as a significant prognostic predictor in patients with uHCC treated with TACE, lenvatinib, or PD-1 inhibitors.[21–23]

Recently, a novel prognostic score combining SII and PNI (SII-PNI score) has been employed to predict outcomes in various malignancies, including gastric cancer, lung cancer, urothelial carcinoma, and gestational trophoblastic neoplasia.[24–30] However, the prognostic value of the SII-PNI score in patients with uHCC treated with triple therapy remains unclear. Therefore, this multicenter retrospective study aimed to explore the predictive effect of the SII-PNI score for survival and tumor response in patients with uHCC receiving triple therapy.

Materials and Methods

Study Design and Patients

This multicenter, retrospective study reviewed data from patients with uHCC treated with triple therapy at eight tertiary hospitals in China between August 2018 and July 2023. The participating hospitals included Fujian Provincial Hospital, the First Affiliated Hospital of Fujian Medical University, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhongshan Hospital of Xiamen University, First Affiliated Hospital of Xiamen University, Fujian Medical University Union Hospital, the Second Affiliated Hospital of Nanchang University, and Eastern Hepatobiliary Surgery Hospital. This study adhered to the ethical guidelines outlined in the Declaration of Helsinki. The study design received approval from the Institutional Review Board of each center, and written informed consent was obtained from each patient before treatment initiation.

Diagnosis of HCC was based on clinical criteria or histopathology in accordance with the China Liver Cancer staging system.[3] Tumor staging was determined using the Barcelona Clinic Liver Cancer (BCLC) staging system.[4] The diagnosis of uHCC was established by a multidisciplinary team (MDT). The inclusion criteria for this study were: 1) diagnosis of uHCC and receipt of triple therapy as initial treatment; 2) age between 18 and 75 years; 3) Child-Pugh class A; and 4) BCLC stage B or C. The exclusion criteria included: 1) the presence of other malignancies; 2) a history of autoimmune disease; 3) Eastern Cooperative Oncology Group performance status score > 1; and 4) missing critical data.

Triple Therapy Procedure

In this study, all patients underwent conventional TACE. The right femoral artery was punctured using the Seldinger technique, and a 5F catheter was inserted. Tumor-feeding arteries were identified through hepatic artery angiography. A mixture of pirarubicin and lipiodol (5–20 mL) was infused into the tumor-feeding arteries via superselective catheterization, followed by embolization with gelatin sponge granules. TACE was repeated on demand every 4–6 weeks, based on the presence of viable tumors and the patient's hepatic function.

Within 3–14 days following the initial TACE procedure, lenvatinib and PD-1 inhibitors were initiated. Lenvatinib was administered orally at a dose of 8 mg/day (body weight <60 kg) or 12 mg/day (body weight ≥60 kg). PD-1 inhibitors (pembrolizumab 200 mg, camrelizumab 200 mg, toripalimab 240 mg, tislelizumab 200 mg, sintilimab 200 mg, or penpulimab 200 mg) were administered via injection every 3 weeks. Both lenvatinib and PD-1 inhibitors were suspended

3 days before and after each TACE procedure. Antiviral therapy, including entecavir or tenofovir, was provided to patients with hepatitis B virus (HBV) infection.

Treatment-related adverse events (TRAEs) were monitored and recorded throughout the treatment, based on the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0.

Follow-up

Routine follow-up was conducted for each patient every 4–8 weeks. The resectability of HCC was assessed by the MDT at each visit, and conversion surgery was considered for patients with resectable tumors.[31] Before conversion surgery, lenvatinib and PD-1 inhibitors were discontinued for 1 and 4 weeks, respectively. After conversion surgery, lenvatinib and PD-1 inhibitors were administered for 3–12 months as postoperative adjuvant therapy. For patients who did not undergo conversion surgery, triple therapy continued until there was unacceptable toxicity, disease progression, or treatment refusal. Subsequent treatment options were determined through MDT discussions and the patient's preferences.

Outcomes

The primary endpoint of this study was OS, defined as the time from the initiation of triple therapy to death from any cause. The secondary endpoints included progression-free survival (PFS), ORR, and disease control rate (DCR), assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[32] PFS was defined as the time from the initiation of triple therapy to either disease progression or death from any cause. Patients were censored at the last follow-up if no events occurred. ORR was the proportion of patients achieving complete response or partial response as the best tumor response. DCR was the proportion of patients with complete response, partial response, or stable disease. The data cutoff date was April 31, 2024.

Statistical Analysis

No formal sample size calculation was performed due to the retrospective nature of the study. All eligible patients who met the inclusion and exclusion criteria were included. Continuous variables were reported as median (interquartile range [IQR]) and compared using the Kruskal–Wallis test. Categorical variables were expressed as numbers (percentages) and compared using Pearson's chi-square test.

To enhance clinical interpretability, age, alpha-fetoprotein (AFP), tumor number, and tumor diameter were dichotomized according to clinically meaningful cutoff values. The albumin-bilirubin (ALBI) score was calculated as: $\log_{10}(\text{bilirubin}) \times 0.66 + \text{albumin} \times (-0.085)$. ALBI grades were defined as follows: grade 1, ALBI score ≤ -2.60; grade 2, $-2.60 <$ ALBI score ≤ -1.39; and grade 3, ALBI score > -1.39. Since no patients were classified as ALBI grade 3 in this study, grades 2 and 3 were combined for analysis.

Because there is no universally accepted cut-off value, X-tile software (version 3.6.1, Yale University) was used to determine the optimal cut-off values for SII and PNI based on OS.[33] All possible cut-points were calculated, and the value that generated the largest χ^2 value in the Log rank test was selected as the optimal cut-off by X-tile software. SII and PNI were calculated as follows: SII = platelet count (×10^9/L) × neutrophil count (×10^9/L)/lymphocyte count (×10^9/L); PNI = albumin (g/L) + 5 × lymphocyte count (×10^9/L).[23] Spearman correlation analysis was performed to assess the relationship between SII and PNI levels. The SII-PNI score was categorized as follows: score of 0, low SII (≤cut-off value) and high PNI (>cut-off value); score of 1, either high SII-high PNI or low SII-low PNI; score of 2, high SII and low PNI.

OS and PFS were estimated and compared using Kaplan-Meier curves with the Log rank test. The reverse Kaplan-Meier method was applied to calculate the median follow-up time. Univariate and multivariate Cox proportional hazards regression models were applied to identify the predictors of OS and PFS. The multivariate analysis was conducted using the forced entry method, with variables selected based on clinical importance and statistical significance in univariate analysis ($p < 0.05$). The proportional hazards assumption was tested using the Schoenfeld residual test, and multicollinearity was evaluated with the variance inflation factor. Furthermore, the prognostic value of the SII-PNI score was evaluated by subgroup analyses with interaction tests, and results were shown as forest plots. All statistical analyses were performed using R Studio, version 2024.04.2+764 (R Studio Inc., Boston, MA, USA). A p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 290 patients were included in this study (Supplementary Figure 1). The baseline demographic and clinical characteristics of the entire study population are summarized in Table 1. The median age was 56 years (IQR 50–64), with 253 (87.2%) male patients, and most patients had HBV infections (259/290, 89.3%). At diagnosis, 77 (26.6%) and 213 (73.4%) patients were classified as BCLC stage B and C, respectively. The median SII and PNI levels were 534.1 (IQR 292.6–901.7) and 47.4 (IQR 42.2–51.8), respectively. Additionally, 123 (42.4%) patients had a maximum tumor size of ≥10 cm, while 188 (64.8%) patients had three or more tumor lesions. Macrovascular invasion was identified in more than half of patients (171/290, 59.0%), and extrahepatic metastasis was observed in 55 (19.0%) patients.

Table 1 Baseline Demographic and Clinical Characteristics of Patients

Characteristics	Patients (n = 290)
Age, years	56 (50–64)
Age	
< 65 years	223 (76.9)
≥ 65 years	67 (23.1)
Sex	
Female	37 (12.8)
Male	253 (87.2)
HBV infection	
No	31 (10.7)
Yes	259 (89.3)
ECOG PS	
0	226 (77.9)
1	64 (22.1)
BCLC stage	
B	77 (26.6)
C	213 (73.4)
Child-Pugh score	
5	212 (73.1)
6	78 (26.9)
ALBI grade	
1	144 (49.7)
2 and 3	146 (50.3)
AFP levels	
< 400 ng/mL	143 (49.3)
≥ 400 ng/mL	147 (50.7)
Platelet count, ×10^9/L	187.0 (137.8–245.0)
Neutrophil count, ×10^9/L	3.9 (2.9–5.5)
Lymphocyte count, ×10^9/L	1.4 (1.1–1.8)
Albumin level, g/L	40.0 (35.8–43.4)
SII level	534.1 (292.6–901.7)
PNI level	47.4 (42.2–51.8)
Maximum tumor size	
< 10 cm	167 (57.6)
≥ 10 cm	123 (42.4)
Tumor number	
< 3	102 (35.2)
≥ 3	188 (64.8)

(*Continued*)

Table 1 (Continued).

Characteristics	Patients (n = 290)
Macrovascular invasion	
No	119 (41.0)
Yes	171 (59.0)
Extrahepatic metastasis	
No	235 (81.0)
Yes	55 (19.0)

Notes: Data are presented as median (interquartile range) or number (%).
Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic for Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

Spearman correlation analysis revealed a significant negative correlation between the SII and PNI levels (r = −0.225, $p < 0.001$; Figure 1). The optimal cut-off values were 525.9 for SII and 44.0 for PNI (Supplementary Figure 2). Consequently, the SII-PNI score was categorized into three groups: score of 0 (n = 105), low SII (≤525.9) and high PNI (>44.0); score of 1 (n = 124), either high SII-high PNI or low SII-low PNI; and score of 2 (n = 61), high SII and low PNI. The baseline demographic and clinical characteristics were compared among patients with different SII-PNI scores (Supplementary Table 1). No significant differences were observed among the three groups concerning age, sex, HBV infection, AFP levels, tumor number, or extrahepatic metastasis. However, significant differences were found in median

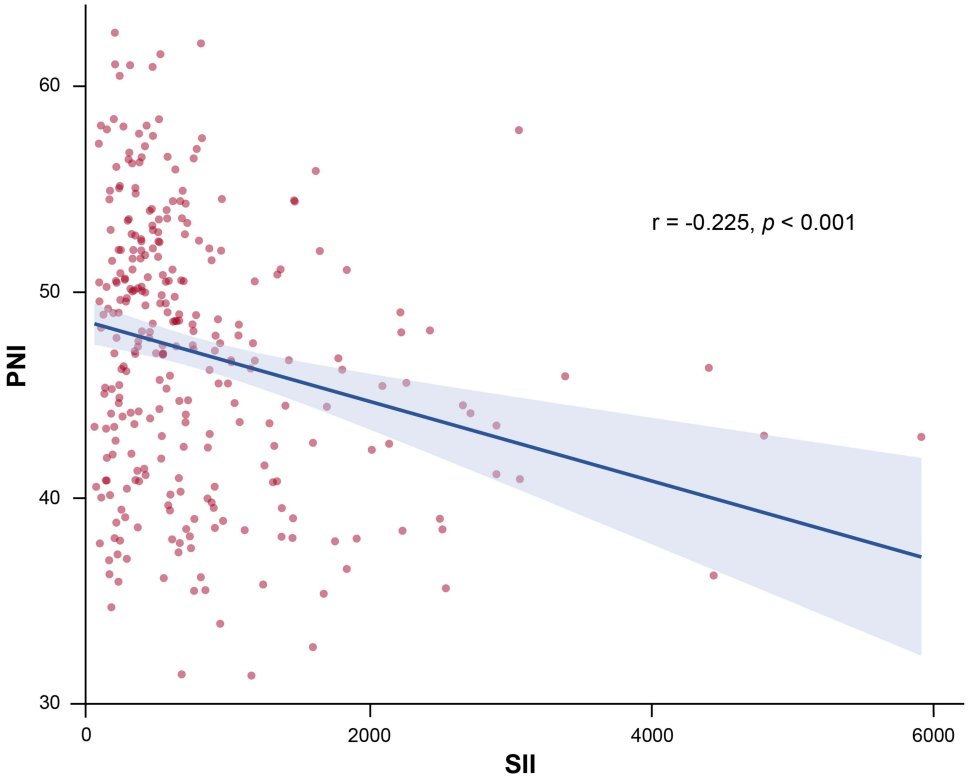

Figure 1 Correlation analysis between the SII and PNI levels.
Abbreviations: PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

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age, Eastern Cooperative Oncology Group performance status, BCLC stage, Child-Pugh score, ALBI grade, maximum tumor size, and macrovascular invasion.

Treatment Protocol

A median of two sessions (IQR 1–3) of TACE were administered. The median number of cycles for PD-1 inhibitors was 12 (IQR 8–22), while the median duration of lenvatinib treatment was 10.1 months (IQR 7.6–16.3). A total of six different PD-1 inhibitors were employed in this study: camrelizumab (n = 112), sintilimab (n = 74), tislelizumab (n = 69), toripalimab (n = 15), pembrolizumab (n = 12), and penpulimab (n = 8). Conversion surgery was performed in 106 (36.6%) patients.

Safety Profile

As shown in Supplementary Table 2, a total of 87.2% (253/290) of patients experienced TRAEs of any grade, with 28.3% (82/290) reporting grade 3–5 TRAEs. The most common grade 3–5 TRAEs included abnormal liver function (19.0%), pyrexia (2.4%), hand-foot syndrome (2.4%), hypertension (1.7%), thrombocytopenia (1.4%), skin rash (1.0%), fatigue (0.7%), diarrhea (0.7%), and proteinuria (0.7%).

Dose reductions or interruptions of lenvatinib occurred in 28 (9.7%) patients, while interruptions of PD-1 inhibitors occurred in 11 (3.8%) patients due to TRAEs. Nine (3.1%) patients discontinued PD-1 inhibitors, and 13 (4.5%) patients discontinued lenvatinib due to TRAEs. In addition, three (1.0%) patients experienced treatment-related deaths.

Tumor Response

According to the mRECIST, the best tumor responses observed were: complete response (71/290, 24.5%), partial response (150/290, 51.7%), stable disease (39/290, 13.4%), and progressive disease (30/290, 10.3%). The ORR was 76.2%, while the DCR was 89.7%. The ORRs for SII-PNI scores of 0, 1, and 2 were 83.8%, 76.6%, and 62.3%, respectively ($p = 0.007$). The corresponding DCRs for these groups were 95.2%, 90.3%, and 78.7%, respectively ($p = 0.003$; Table 2).

Survival Outcomes

The median follow-up period was 25.0 months (95% confidence interval [CI], 22.8–26.7). The median OS was 30.7 months (95% CI, 26.6–not reached), with 12-, 24-, and 36-month OS rates of 81.4%, 57.2%, and 45.4%, respectively (Supplementary Figure 3A). The median PFS was 16.9 months (95% CI, 14.7–21.7), with corresponding 12-, 24-, and 36-month PFS rates of 63.1%, 41.3%, and 32.5% (Supplementary Figure 3B).

Survival Outcomes According to SII-PNI Score

The median OS was not reached for patients with SII-PNI score of 0, while it was 28.0 months (95% CI, 23.1–not reached) for those with score of 1, and 19.7 months (95% CI, 14.0–not reached) for those with score of 2 ($p < 0.001$; Figure 2A). The 36-month OS rates were 60.0%, 39.1%, and 33.3% for patients with SII-PNI scores of 0, 1, and 2, respectively.

Table 2 Relationship Between SII-PNI Score and Tumor Response

Best Response	SII-PNI Score		
	0 (n = 105)	1 (n = 124)	2 (n = 61)
Objective response, n (%)			$p = 0.007$
Yes (CR/PR)	88 (83.8)	95 (76.6)	38 (62.3)
No (SD/PD)	17 (16.2)	29 (23.4)	23 (37.7)
Disease control, n (%)			$p = 0.003$
Yes (CR/PR/SD)	100 (95.2)	112 (90.3)	48 (78.7)
No (PD)	5 (4.8)	12 (9.7)	13 (21.3)

Abbreviations: CR, complete response; PD, progressive disease; PNI, prognostic nutritional index; PR, partial response; SD, stable disease; SII, systemic immune-inflammation index.

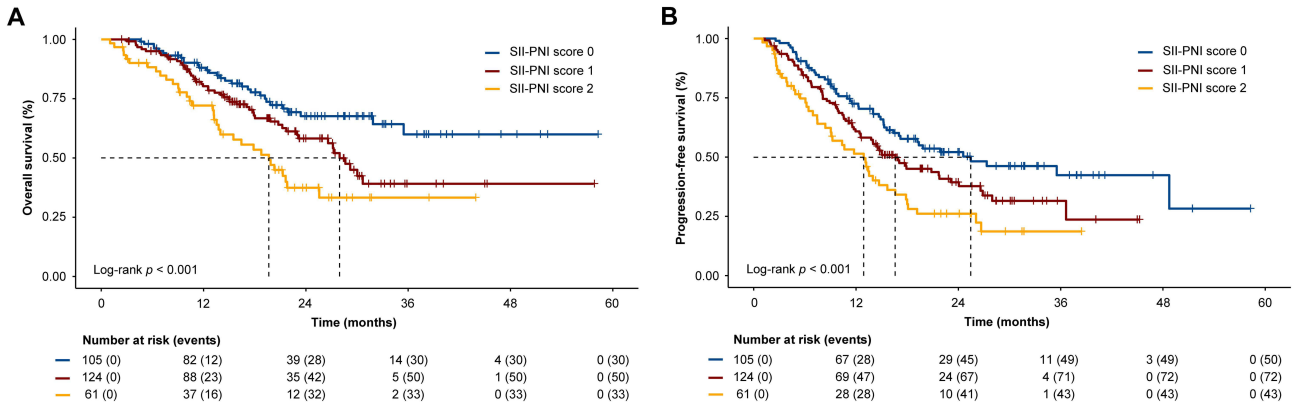

Figure 2 Kaplan–Meier curves according to the SII-PNI score. (**A**) Overall survival. (**B**) Progression-free survival.
Abbreviations: PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

Similarly, PFS was significantly stratified by the SII-PNI score (Figure 2B). The median PFS for patients with SII-PNI scores of 0, 1, and 2 were 25.5 months (95% CI, 17.0–not reached), 16.6 months (95% CI, 12.5–24.1), and 12.9 months (95% CI, 9.0–16.6), respectively ($p < 0.001$). In addition, the 36-month PFS rates were 42.4%, 31.5%, and 18.6% for the respective groups.

Predictors of Overall Survival

In the univariate analysis, variables associated with shorter OS included AFP levels ≥400 ng/mL ($p = 0.021$), maximum tumor size ≥10 cm ($p = 0.010$), tumor number ≥3 ($p = 0.046$), extrahepatic metastasis ($p < 0.001$), SII-PNI score of 1 ($p = 0.031$), and SII-PNI score of 2 ($p < 0.001$; Table 3).

Table 3 Univariate and Multivariate Analysis for Overall Survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age						
< 65 years	Reference					
≥ 65 years	0.82	0.52–1.29	0.391			
Sex						
Female	Reference					
Male	0.97	0.56–1.70	0.926			
HBV infection						
No	Reference					
Yes	0.98	0.54–1.78	0.948			
ECOG PS						
0	Reference					
1	1.16	0.75–1.78	0.510			
Child-Pugh score						
5	Reference			Reference		
6	1.32	0.89–1.96	0.170	0.70	0.38–1.28	0.248
ALBI grade						
1	Reference			Reference		
2 and 3	1.20	0.83–1.74	0.331	0.88	0.52–1.47	0.617
AFP levels						
< 400 ng/mL	Reference			Reference		
≥ 400 ng/mL	1.55	1.07–2.26	0.021	1.26	0.84–1.88	0.261

(*Continued*)

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Table 3 (Continued).

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Maximum tumor size						
< 10 cm	Reference			Reference		
≥ 10 cm	1.62	1.12–2.34	0.010	1.14	0.76–1.71	0.522
Tumor number						
< 3	Reference			Reference		
≥ 3	1.56	1.01–2.40	0.046	1.54	0.99–2.41	0.058
Macrovascular invasion						
No	Reference			Reference		
Yes	1.43	0.98–2.10	0.065	1.44	0.96–2.18	0.081
Extrahepatic metastasis						
No	Reference			Reference		
Yes	3.05	2.06–4.52	<0.001	2.96	1.96–4.46	<0.001
SII-PNI score						
0	Reference			Reference		
1	1.65	1.05–2.60	0.031	1.67	1.04–2.67	0.033
2	2.73	1.66–4.49	<0.001	3.52	1.72–7.21	0.001

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HR, hazard ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

The multivariate analysis identified extrahepatic metastasis (hazard ratio [HR], 2.96; 95% CI, 1.96–4.46; $p < 0.001$), SII-PNI score of 1 (HR, 1.67; 95% CI, 1.04–2.67; $p = 0.033$), and SII-PNI score of 2 (HR, 3.52; 95% CI, 1.72–7.21; $p = 0.001$) as independent predictors of OS (Table 3).

Predictors of Progression-Free Survival

The univariate analysis showed that five variables were associated with shorter PFS: AFP levels ≥400 ng/mL ($p = 0.004$), maximum tumor size ≥10 cm ($p = 0.045$), extrahepatic metastasis ($p < 0.001$), SII-PNI score of 1 ($p = 0.041$), and SII-PNI score of 2 ($p < 0.001$; Table 4).

Table 4 Univariate and Multivariate Analysis for Progression-Free Survival

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age						
< 65 years	Reference					
≥ 65 years	0.99	0.69–1.41	0.946			
Sex						
Female	Reference					
Male	0.93	0.59–1.46	0.760			
HBV infection						
No	Reference					
Yes	0.97	0.59–1.58	0.894			
ECOG PS						
0	Reference					
1	1.20	0.83–1.71	0.331			
Child-Pugh score						
5	Reference			Reference		
6	1.29	0.93–1.79	0.126	0.80	0.50–1.27	0.347

(*Continued*)

Table 4 (Continued).

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
ALBI grade						
1	Reference			Reference		
2 and 3	1.23	0.90–1.67	0.188	0.95	0.62–1.44	0.794
AFP levels						
< 400 ng/mL	Reference			Reference		
≥ 400 ng/mL	1.58	1.16–2.16	0.004	1.48	1.06–2.07	0.020
Maximum tumor size						
< 10 cm	Reference			Reference		
≥ 10 cm	1.37	1.01–1.86	0.045	1.08	0.77–1.50	0.657
Tumor number						
< 3	Reference			Reference		
≥ 3	1.32	0.94–1.85	0.105	1.35	0.96–1.92	0.087
Macrovascular invasion						
No	Reference			Reference		
Yes	1.15	0.84–1.57	0.381	1.06	0.75–1.51	0.727
Extrahepatic metastasis						
No	Reference			Reference		
Yes	2.14	1.51–3.04	<0.001	2.14	1.49–3.06	<0.001
SII-PNI score						
0	Reference			Reference		
1	1.46	1.02–2.10	0.041	1.56	1.06–2.29	0.024
2	2.22	1.47–3.35	<0.001	2.64	1.50–4.65	0.001

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HR, hazard ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

The multivariate analysis revealed that AFP levels ≥400 ng/mL (HR, 1.48; 95% CI, 1.06–2.07; $p = 0.020$), extrahepatic metastasis (HR, 2.14; 95% CI, 1.49–3.06; $p < 0.001$), SII-PNI score of 1 (HR, 1.56; 95% CI, 1.06–2.29; $p = 0.024$), and SII-PNI score of 2 (HR, 2.64; 95% CI, 1.50–4.65; $p = 0.001$) were independent predictors of PFS (Table 4).

Prognostic Value of SII-PNI Score in Different Subgroups

Exploratory subgroup analyses were conducted to assess whether the prognostic value of the SII-PNI score observed in the overall cohort remained consistent across different subgroups. In the analysis of OS, no significant interactions were observed in any of the six subgroups, including Child-Pugh score, HBV infection, Eastern Cooperative Oncology Group performance status, BCLC stage, macrovascular invasion, and extrahepatic metastasis (all interaction $p > 0.05$; Supplementary Figure 4). Similarly, the association between the SII-PNI score and PFS was consistent across all subgroups (all interaction $p > 0.05$; Supplementary Figure 5).

Discussion

Recently, various inflammation-based prognostic indicators have been developed and applied to predict outcomes of HCC.[21–23,34] The SII-PNI score is a novel prognostic tool that integrates immune, inflammatory, and nutritional variables. Despite the significant prognostic value of the SII-PNI score demonstrated in multiple cancer types, it has been rarely investigated in HCC. This study evaluated the prognostic value of the SII-PNI score in patients with uHCC treated with triple therapy. Our findings indicate that the SII-PNI score is closely associated with OS, PFS, and tumor response. To our knowledge, this is the first study assessing the utility of the SII-PNI score in patients with uHCC treated with triple therapy.

The systemic inflammatory response is intricately linked to tumorigenesis, invasion, and metastasis through various mechanisms.[15,35] Higher SII levels reflect increased platelet/neutrophil counts and/or decreased lymphocyte counts. Evidence suggests that neutrophils can enhance cancer cell invasion, proliferation, and metastasis.[36] Furthermore, neutrophils may suppress the immune response, aiding cancer cells in evading immune surveillance.[37,38] Platelets, known for their multifaceted roles in hemostasis, have also been implicated in promoting tumor growth and metastasis via multiple mechanisms.[39] Conversely, a decrease in lymphocyte counts suggests impaired immune surveillance and a compromised host immune response.[40]

Nutritional status significantly influences disease progression and survival in patients with cancer.[19,20,41] Lower PNI levels result from decreased serum albumin and/or lymphocyte levels. Hypoalbuminemia not only indicates poor nutritional status but also reflects liver dysfunction in patients with HCC.[42] Additionally, previous studies have shown that systemic inflammatory responses correlate with declining nutritional status.[43] Therefore, the integration of SII and PNI may provide a more comprehensive assessment of the immune-inflammatory-nutritional status of patients, enhancing predictive ability for cancer prognosis.

There are complex synergistic interactions among TACE, lenvatinib, and PD-1 inhibitors, but the exact mechanisms remain unclear.[6,7,44–46] TACE may facilitate the release of tumor-specific antigens and pro-inflammatory cytokines.[47] Lenvatinib exhibits immunomodulatory effects by reducing tumor-associated macrophage infiltration and increasing activated CD8+ T cell proportions.[48] PD-1 inhibitors disrupt the PD-1/PD-L1 interaction, reinstating CD8+ T cell function and thereby activating antitumor immunity.[44] A higher SII-PNI score is indicative of a predominance of immune-suppressive cells and inhibition of effector immune response cells, suggesting an immunosuppressive microenvironment. Meanwhile, a higher SII-PNI score reflects poorer nutritional status and liver function, resulting in worse treatment tolerance. Therefore, it is reasonable to utilize the SII-PNI score to predict prognosis in patients with uHCC receiving triple therapy.

Tumor response is critical in assessing treatment efficacy. In our previous study, a nomogram incorporating AFP levels, portal vein tumor thrombus, tumor number, and size could predict early tumor response to triple therapy in patients with uHCC.[49] Moreover, we identified that changes in AFP and des-gamma-carboxyprothrombin levels were associated with tumor response to triple therapy.[50] In this study, the SII-PNI score not only predicted OS and PFS but also showed a significant association with tumor response. The results showed that lower SII-PNI score was correlated with improved ORR and DCR. The SII-PNI score derives from laboratory indicators routinely measured in clinical practice, making it a simple, accessible, and cost-effective tool for identifying patients who are likely to benefit from triple therapy. These findings can aid in optimizing treatment strategies and facilitate clinical decision-making for uHCC.

However, this study has certain limitations. Firstly, it is a retrospective study, which may introduce potential bias. In addition, the dynamics of SII and PNI were not recorded, and a comparison of the SII-PNI score with other inflammatory variables could not be conducted. Second, considering the limited sample size, we did not further divide the cohort into training and validation sets in this study. Therefore, further external validation through large-scale prospective studies with long-term follow-up is warranted. Thirdly, using different PD-1 inhibitors in this study may lead to treatment heterogeneity and variable efficacy. Lastly, since most patients in this study were infected with HBV, further validation is required to determine the applicability of the SII-PNI score for patients with other etiologies of HCC.

Conclusion

In conclusion, the SII-PNI score is a simple, accessible, and cost-effective prognostic tool for predicting OS, PFS, and tumor response in patients with uHCC treated with triple therapy. This score aids in optimizing clinical decision-making for uHCC; however, further validation of these findings is warranted.

Abbreviations

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic for Liver Cancer; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; MDT, multidisciplinary team; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PNI, prognostic nutritional index; PR, partial response; SD,

stable disease; SII, systemic immune-inflammation index; TACE, transcatheter arterial chemoembolization; TRAEs, treatment-related adverse events; uHCC, unresectable hepatocellular carcinoma.

Data Sharing Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author Mao-Lin Yan.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki with approval from the Institutional Review Board of Fujian Provincial Hospital (approval number: K2024-09-046). Written informed consent was obtained from each patient before treatment initiation.

Author Contributions

All authors reviewed and approved the final version of the manuscript. 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; All authors took part in drafting, revising or critically reviewing the article; All authors gave final approval of the version to be published; All authors 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 report no conflicts of interest in this work.

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