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Prognostic Significance of Preoperative Inflammatory and Liver Fibrosis Markers in Hepatocellular Carcinoma

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Purpose: Prognostic heterogeneity remains a challenge in hepatocellular carcinoma (HCC) following curative resection. Inflammatory markers such as the platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), and systemic inflammation response index (SIRI), as well as liver fibrosis markers including gamma-glutamyltransferase-to-lymphocyte ratio (GLR), gamma-glutamyltransferase-to-platelet ratio (GPR), and AST-to-ALT ratio (AAR), have shown prognostic potential. This study aimed to evaluate their predictive value for survival after resection.

Methods: We retrospectively analyzed 187 patients with HCC who underwent curative resection between 2008 and 2022. Preoperative inflammatory and fibrosis markers, along with clinical variables, were assessed using univariate and multivariate Cox regression for overall survival (OS) and disease-free survival (DFS). Kaplan-Meier analysis and nomogram models were used to estimate 1-, 3-, and 5-year survival.

Results: Multivariate analysis identified elevated SII, AAR, low PNI, tumor thrombus, and postoperative complications as independent predictors of poor OS, while only tumor thrombus and SIRI independently predicted DFS. SII, AAR, and PNI were also significantly associated with aggressive tumor characteristics. Patients with all three adverse markers (high SII, high AAR, low PNI) showed significantly poorer OS and DFS. A prognostic score incorporating these markers and nomogram models were constructed to predict OS and DFS after resection.

Conclusion: SII, AAR, and PNI are independent prognostic indicators for HCC following resection. The proposed prognostic score and nomograms may assist in individualized survival assessment and postoperative decision-making.

Keywords: systemic immune-inflammation index, prognostic nutritional index, AST-to-ALT ratio, hepatectomy

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide and ranks as the third leading cause of cancer-related death.[1] Curative resection remains a cornerstone treatment for patients with early- to intermediate-stage HCC, offering the potential for long-term survival. However, postoperative recurrence and metastasis remain major obstacles, substantially limiting overall outcomes.[2] This highlights the urgent need for reliable prognostic biomarkers to improve risk stratification and guide individualized postoperative management.

Chronic inflammation plays a pivotal role in hepatocarcinogenesis.[3] Recent evidence underscores the contribution of systemic inflammation and liver fibrosis to the initiation and progression of HCC.[4,5] For instance, inflammation-induced hepatocyte injury can trigger compensatory proliferation, thereby increasing mutation rates and promoting malignant transformation.[3] Simultaneously, sustained hepatic inflammation drives fibrosis progression and ultimately cirrhosis—a well-established risk factor for HCC, with approximately 70–90% of cases arising in cirrhotic livers.[6,7] Consequently, peripheral blood markers reflecting systemic inflammatory status and hepatic fibrosis have gained attention as promising prognostic indicators in HCC.

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Although staging systems such as BCLC, TNM, and ALBI are widely applied in clinical practice, each has notable limitations. BCLC provides limited individualized prognostication,[8] TNM focuses only on tumor burden without accounting for liver reserve,[9] and ALBI, while objective, does not fully capture portal hypertension or disease heterogeneity.[10] These shortcomings underscore the need for novel, easily accessible biomarkers to complement existing systems and improve risk stratification.

Several inflammation- and fibrosis-related biomarkers have been proposed in recent years, including the platelet-to-lymphocyte ratio (PLR),[11] systemic immune-inflammation index (SII), systemic inflammation response index (SIRI),[12] prognostic nutritional index (PNI),[13] gamma-glutamyl transpeptidase-to-lymphocyte ratio (GLR),[14] gamma-glutamyl transpeptidase-to-platelet ratio (GPR),[15] and the aspartate aminotransferase-to-alanine aminotransferase ratio (AAR). These indicators are readily available from routine laboratory tests, cost-effective, and reflective of a patient's immune, metabolic, nutritional, and hepatic condition. However, few studies have comprehensively assessed the prognostic value of these markers in combination—particularly in predicting both survival and recurrence after curative resection. Therefore, this study aimed to evaluate the prognostic significance of preoperative inflammatory and fibrosis-related markers in HCC patients undergoing curative hepatectomy.

Materials and Methods

Study Population

We retrospectively analyzed 187 patients with hepatocellular carcinoma (HCC) who underwent curative-intent liver resection at Zhejiang Cancer Hospital between 2008 and 2022. The diagnosis of HCC was confirmed by histopathological examination, and tumors were staged according to the 8th edition of the TNM classification by the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC).[16] Preoperative baseline data, including demographic characteristics, laboratory findings (hematologic and biochemical parameters), and imaging results, were collected. Imaging assessments included abdominal ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) performed prior to surgery.

The inclusion criteria were: (1) age ≥18 years; (2) histologically confirmed HCC classified as stage I, II, IIIA, or IIIB based on the 8th edition of the UICC/AJCC TNM staging system; (3) receipt of curative-intent hepatectomy; (4) availability of complete preoperative laboratory data, including inflammatory and liver fibrosis markers; and (5) complete follow-up information.

Exclusion criteria included: (1) TNM stage IIIC, IVA, or IVB disease; (2) receipt of any preoperative anti-cancer treatment, including percutaneous ablation, transarterial chemoembolization (TACE), systemic chemotherapy, or radiotherapy; (3) presence of acute infection or autoimmune disease that could influence inflammatory biomarkers; and (4) coexisting malignancies or a history of malignancy within the previous five years.

In most patients, preoperative blood samples were collected within 14 days before surgery and were used to determine white blood cell count, neutrophil count, monocyte count, lymphocyte count, platelet count, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) levels. The following indices were calculated using the respective formulas:

SII = (Platelet count [$\times 10^9$/L] × Neutrophil count [$\times 10^9$/L]) / Lymphocyte count [$\times 10^9$/L]; PNI = 10 × Serum Albumin [g/dL] + 5 × Total Lymphocyte count [$\times 10^9$/L]; SIRI = Neutrophil count [$\times 10^9$/L] × Monocyte count [$\times 10^9$/L] / Lymphocyte count [$\times 10^9$/L]; PLR = Platelet count [$\times 10^9$/L] / Lymphocyte count [$\times 10^9$/L]; GLR = GGT (U/L) / Lymphocyte count [$\times 10^9$/L]; GPR = GGT (U/L) / Platelet count [$\times 10^9$/L] count and AAR = AST (U/L) / ALT (U/L).

Patient Follow-up

Postoperative follow-up was conducted every 2–3 months during the first two years and every 3–6 months thereafter via outpatient visits or telephone interviews. Follow-up assessments included physical examinations, laboratory testing, and imaging studies such as ultrasound or CT scans. Tumor recurrence was diagnosed based on clinical, radiological, or pathological findings. Overall survival (OS) was defined as the time from surgery to death from any cause. For patients lost to follow-up, the date of the last contact was used. Disease-free survival (DFS) was defined as the time from surgery to the date of recurrence or last follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Median values were used as the cut-off thresholds for SII, PNI, SIRI, PLR, GLR, GPR, and AAR to stratify patients into high and low groups. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution, and were compared using the Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Survival analyses were conducted using the Kaplan–Meier method, and differences between groups were evaluated using the Log rank test. Variables identified as significant in univariate analyses were included in multivariate Cox proportional hazards models to identify independent predictors of OS and DFS. Nomograms for predicting 1-, 3-, and 5-year OS and DFS were developed using R software version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). *P* values <0.05 was considered statistically significant.

Results

Baseline Characteristics

The study cohort, as shown in Table 1, comprised 156 male patients (83.4%) and 31 female patients (16.6%), with a mean age of 60 years (range, 52–65 years). The median body mass index (BMI) was 22.9 kg/m^2 (interquartile range [IQR], 21.2–24.5 kg/m^2). During follow-up, tumor recurrence occurred in 157 patients (84.0%), and 78 patients (41.7%) died. Hepatitis B surface antigen (HBsAg) positivity was observed in 173 patients (92.5%), and cirrhosis was present in 145 patients (77.5%). Common comorbidities included diabetes (n = 23, 12.2%) and hypertension (n = 62, 33.1%). Additionally, 84 patients (44.9%) had a history of smoking, and 65 patients (34.7%) reported alcohol consumption. According to the TNM classification, 152 patients

Table 1 Baseline Characteristics of Patients Undergoing Curative Hepatectomy for HCC

Clinical Variables	Overall (n=187) (%)
Patient factors	
Male (n, %)	156 (83.4%)
Age (years; mean ± SD)	60 (52–65)
BMI	22.9 (21.2–24.5)
Smoking (n, %)	84 (44.9%)
Drinking (n, %)	65 (34.7%)
Diabetes (n, %)	23 (12.2%)
Hypertension (n, %)	62 (33.1%)
Coronary disease (n, %)	3 (1.6%)
Hepatitis B (n, %)	173 (92.5%)
Cirrhosis (n, %)	145 (77.5%)
Laboratory data	
SII	371.6 (213.9–613.9)
PNI	44.0 (41.2–47.0)
SIRI	0.8 (0.5–1.3)
PLR	104 (79.2–145.6)
GLR	38.0 (20.0–73.8)
GPR	0.3 (0.2–0.7)
AAR	1.0 (0.8–1.3)
Tumor factors	
I–II Stage	152 (81.3%)
III Stage	35 (18.7%)
Tumor size >5cm (n, %)	59 (31.6%)
Tumor count >1 (n, %)	25 (13.4%)
Tumor thrombus (n, %)	38 (20.3%)

(*Continued*)

Table 1 (Continued).

Clinical Variables	Overall (n=187) (%)
Surgical factors	
Blood loss (mL)	200 (100–400)
Complication (n, %)	9 (4.8%)
Follow-up	
Mortality (n, %)	78 (41.7%)
Recurrence (n, %)	157 (84.0%)
OS (days, median [IQR])	1082 (813–1552)
DFS (days, median [IQR])	581 (227–956)

Abbreviations: BMI, Body Mass Index; SII, Systemic Immune-Inflammation Index; PNI, prognostic nutritional index; SIRI, Systemic Inflammation Response Index; PLR, platelet-to-lymphocyte ratio; GLR, gamma-glutamyl transpeptidase-to-lymphocyte ratio; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio; OS, overall survival; DFS, disease-free survival.

(81.3%) were classified as stage I–II, while 35 patients (18.7%) were stage III. Tumors with a diameter ≥ 50 mm were observed in 59 patients (31.6%), and multiple tumors (>1 lesion) were present in 25 patients (13.4%). Tumor thrombus was detected in 38 patients (20.3%). The median estimated blood loss (EBL) was 200 mL (IQR, 100–400 mL). Postoperative complications occurred in 9 patients (4.8%). At the time of analysis, 41.7% of patients had died and 84.0% experienced recurrence. The median OS was 1082 days (range, 813–1552 days), and the median DFS was 581 days (range, 227–956 days).

Independent Prognostic Factors for HCC

The results of the Cox proportional hazards regression analysis for OS are summarized in Table 2. In univariate analysis, cirrhosis, elevated SII, PNI, PLR, GLR, AAR, tumor size > 5 cm, multiple tumors (>1 lesion), tumor thrombus, and postoperative complications were identified as potential prognostic factors for OS. However, multivariate analysis

Table 2 Univariate and Multivariate Analysis of Prognostic Factors for Overall Survival

Variable	Univariate HR (95% CI)	P value (Univ)	Multivariate HR (95% CI)	P value (Multiv)
Age (years)	1.011[0.988–1.034]	0.348		
Male	0.827[0.470–1.456]	0.510		
BMI	0.946[0.873–1.025]	0.172		
Hepatitis B	1.198[0.436–3.295]	0.726		
Cirrhosis	0.568[0.329–0.980]	0.042	0.754[0.415–1.369]	0.353
SII≥371.6	1.876[1.181–2.981]	0.008	1.937[1.077–3.486]	0.027
PNI≥44.0	0.413[0.249–0.687]	0.001	0.389[0.224–0.675]	0.001
SIRI≥0.8	1.152[0.733–1.811]	0.540		
PLR≥104.0	1.849[1.175–2.910]	0.008	1.239[0.700–2.192]	0.462
GLR≥38.0	1.615[1.029–2.537]	0.037	1.390[0.858–2.254]	0.181
GPR≥0.3	1.092[0.698–1.710]	0.700		
AAR≥1.0	1.618[1.022–2.563]	0.040	1.927[1.177–3.156]	0.009
Tumor size ≥5cm	2.413[1.500–3.882]	<0.001	1.451[0.849–2.482]	0.174
Tumor count>1	1.944[1.116–3.385]	0.019	1.775[0.997–3.162]	0.051
Tumor thrombus	2.251[1.389–3.649]	0.001	2.006[1.141–3.526]	0.016
Blood loss (mL)	1.000[1.000–1.001]	0.270		
Complication	2.329[1.004–5.402]	0.049	3.870[1.576–9.502]	0.003

Abbreviations: BMI, Body Mass Index; SII, Systemic Immune-Inflammation Index; PNI, prognostic nutritional index; SIRI, Systemic Inflammation Response Index; PLR, platelet-to-lymphocyte ratio; GLR, gamma-glutamyl transpeptidase-to-lymphocyte ratio; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio.

revealed that only elevated SII (hazard ratio [HR] = 1.94; 95% confidence interval [CI], 1.08–3.49; P = 0.027), low PNI (HR = 0.39; 95% CI, 0.22–0.68; P = 0.001), elevated AAR (HR = 1.93; 95% CI, 1.18–3.16; P = 0.009), tumor thrombus (HR = 2.01; 95% CI, 1.14–3.53; P = 0.016), and postoperative complications (HR = 3.87; 95% CI, 1.58–9.50; P = 0.003) remained independently associated with decreased OS.

Similarly, the Cox proportional hazards regression analysis for DFS is presented in Table 3. Univariate analysis identified age, elevated SII, SIRI, elevated PLR, tumor size > 5 cm, and postoperative complications as potential prognostic factors for DFS. However, multivariate analysis demonstrated that only elevated SIRI (HR = 1.55; 95% CI, 1.01–2.38; P = 0.045) and tumor thrombus (HR = 2.18; 95% CI, 1.44–3.30; P < 0.001) were independently associated with reduced DFS.

Relationship Between Preoperative SII, PNI, and AAR and the Clinicopathological Parameters of HCC

To further investigate the prognostic significance of preoperative SII, PNI, and AAR in patients with HCC undergoing curative resection, we analyzed their associations with 18 clinicopathological variables, as presented in Table 4. A high SII (≥371.6) was significantly more frequent in patients with liver cirrhosis (P = 0.001), hypertension (P = 0.001), elevated SIRI (≥0.8, P < 0.001), PLR (≥104.0, P < 0.001), GPR (≥0.3, P < 0.001), and tumor size ≥5 cm (P = 0.002). Similarly, a high PNI (≥44.0) was significantly associated with BMI ≥22.86 (P = 0.023), hypertension (P = 0.015), elevated GLR (≥38.0, P = 0.003), GPR (≥0.3, P = 0.004), tumor size ≥5 cm (P = 0.004), and multiple tumors (>1 lesions, P = 0.017). Moreover, an elevated AAR (≥1.0) was significantly associated with smoking (P = 0.001) and diabetes (P = 0.037).

The Effect of SII, PNI, and AAR on the Overall Survival and Disease-Free Survival of Patients

Patients were stratified into high and low groups for SII, PNI, and AAR based on their respective median values. Kaplan–Meier survival analysis demonstrated that both OS and DFS were significantly poorer in patients with high SII compared to those with low SII (P < 0.05; Figure 1A and B). Similarly, patients with high AAR showed significantly worse OS than those with low AAR (P < 0.05; Figure 1C), although no significant difference in DFS was observed between the two

Table 3 Univariate and Multivariate Analysis of Prognostic Factors for Disease-Free Survival

Variable	Univariate HR (95% CI)	P value (Univ)	Multivariate HR (95% CI)	P value (Multiv)
Age (years)	1.376[1.001–1.892]	0.049	1.209[0.869–1.681]	0.260
Male	1.032[0.668–1.593]	0.887		
BMI	0.973[0.708–1.336]	0.864		
Hepatitis B	1.039[0.529–2.042]	0.912		
Cirrhosis	0.674[0.450–1.009]	0.056		
SII≥371.6	1.716[1.240–2.373]	0.001	1.155 [0.701–1.904]	0.571
PNI≥44.0	0.882[0.639–1.217]	0.444		
SIRI≥0.8	1.688[1.223–2.328]	0.001	1.548[1.009–2.375]	0.045
PLR≥104.0	1.470[1.068–2.023]	0.018	1.181[0.793–1.758]	0.413
GLR≥38.0	1.308[0.952–1.797]	0.097		
GPR≥0.3	0.929[0.677–1.276]	0.651		
AAR≥1.0	1.228[0.892–1.692]	0.208		
Tumor size ≥5cm	1.483[1.076–2.044]	0.016	1.157[0.817–1.640]	0.412
Tumor count>1	1.263[0.808–1.974]	0.306		
Tumor thrombus	2.079[1.419–3.044]	<0.001	2.179[1.440–3.297]	<0.001
Blood loss (mL)	1.318[0.944–1.840]	0.105		
Complication	1.605[0.786–3.278]	0.194		

Abbreviations: BMI, Body Mass Index; SII, Systemic Immune-Inflammation Index; PNI, prognostic nutritional index; SIRI, Systemic Inflammation Response Index; PLR, platelet-to-lymphocyte ratio; GLR, gamma-glutamyl transpeptidase-to-lymphocyte ratio; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio.

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Table 4 Correlation Between Preoperative SII, PNI, AAR and Clinico-Pathologic Characteristics in HCC

Variable	Case	SII < 371.6	SII ≥ 371.6	P	PNI < 44.0	PNI ≥ 44.0	P	AAR < 1.0	AAR ≥ 1.0	P
Age (yrs)				0.067			0.941			0.124
≥60	94	41(43.6%)	53(56.4%)		47(50.0%)	47(50.0%)		37(39.4%)	57(60.6%)	
<60	93	53(57.0%)	40(43.0%)		46(49.5%)	47(50.5%)		47(50.5%)	46(49.5%)	
Gender				0.310			0.342			0.248
Male	156	81(51.9%)	75(48.1%)		80(51.3%)	76(48.7%)		73(46.8%)	83(53.2%)	
Female	31	13(41.9%)	18(58.1%)		13(41.9%)	18(58.1%)		11(35.5%)	20(64.5%)	
BMI				0.124			0.023			0.084
≥22.86	96	43(44.8%)	53(55.2%)		40(41.7%)	56(58.3%)		49(51.0%)	47(49.0%)	
<22.86	91	51(56.0%)	40(44.0%)		53(58.2%)	38(41.8%)		35(38.5%)	56(61.5%)	
Hepatitis B				0.091			0.564			0.130
Yes	173	90(52.0%)	83(48.0%)		85(49.1%)	88(50.9%)		75(43.4%)	98(56.6%)	
No	14	4(28.6%)	10(71.4%)		8(57.1%)	6(42.9%)		9(64.3%)	5(35.7%)	
Cirrhosis				0.001			0.087			0.086
Yes	145	82(56.6%)	63(43.4%)		77(53.1%)	68(46.9%)		70(48.3%)	75(51.7%)	
No	42	12(28.6%)	30(71.4%)		16(38.1%)	26(61.9%)		14(33.3%)	28(66.6%)	
Smoking				0.160			0.820			0.001
Yes	84	47(56.0%)	37(44.0%)		41(48.8%)	43(51.2%)		49(58.3%)	35(41.7%)	
No	103	47(45.6%)	56(54.4%)		52(50.5%)	51(49.5%)		35(34.0%)	68(66.0%)	
Drinking				0.412			0.052			0.073
Yes	65	30(46.2%)	35(53.8%)		26(40.0%)	39(60.0%)		35(53.8%)	30(46.2%)	
No	122	64(52.5%)	58(47.5%)		67(54.9%)	55(45.1%)		49(40.2%)	73(59.8%)	
Diabetes				0.803			0.845			0.037
Yes	23	11(47.8%)	12(52.2%)		11(47.8%)	12(52.2%)		15(65.2%)	8(34.8%)	
No	164	83(50.6%)	81(49.4%)		82(50.0%)	82(50.0%)		69(42.1%)	95(57.9%)	
Hypertension				0.001			0.015			0.791
Yes	62	20(32.3%)	42(67.7%)		23(37.1%)	39(62.9%)		27(43.5%)	35(56.5%)	
No	125	74(59.2%)	51(40.8%)		70(56.0%)	55(44.0%)		57(45.6%)	68(54.4%)	
SIRI				<0.001			0.610			0.358
≥0.8	96	22(22.9%)	74(77.1%)		46(47.9%)	50(52.1%)		40(41.7%)	56(58.3%)	
<0.8	91	72(79.1%)	19(20.9%)		47(51.6%)	44(48.4%)		44(48.4%)	47(51.6%)	
PLR				<0.001			0.273			0.343
≥104.0	94	18(19.1%)	76(80.9%)		43(45.7%)	51(54.3%)		39(41.5%)	55(58.5%)	
<104.0	93	76(81.7%)	17(18.3%)		50(53.8%)	43(46.2%)		45(48.4%)	48(51.6%)	
GLR				0.941			0.003			0.602
≥38.0	94	47(50.0%)	47(50.0%)		57(60.6%)	37(39.4%)		44(46.8%)	50(53.2%)	
<38.0	93	47(50.5%)	46(49.5%)		36(38.7%)	57(61.3%)		40(43.0%)	53(57.0%)	
GPR				<0.001			0.004			0.182
≥0.3	99	64(64.6%)	35(35.4%)		59(59.6%)	40(40.4%)		49(49.5%)	50(50.5%)	
<0.3	88	30(34.1%)	58(65.9%)		34(38.6%)	54(61.4%)		35(39.8%)	53(60.2%)	
Tumor size				0.002			0.004			0.364
≥5cm	87	33(37.9%)	54(62.1%)		53(60.9%)	34(39.1%)		36(41.4%)	51(58.6%)	
<5cm	100	61(61.0%)	39(39.0%)		40(40.0%)	60(60.0%)		48(48.0%)	52(52.0%)	
Tumor count				0.852			0.017			0.335
>1	25	13(52.0%)	12(48.0%)		18(72.0%)	7(28.0%)		9(36.0%)	16(64.0%)	
=1	162	81(50.0%)	81(50.0%)		75(46.3%)	87(53.7%)		75(46.3%)	87(53.7%)	
Tumor thrombus				0.689			0.136			0.980
Yes	38	18(47.4%)	20(52.6%)		23(60.5)	15(39.5%)		17(44.7%)	21(55.3%)	
No	149	76(51.0%)	73(49.0%)		70(47.0%)	79(53.0%)		67(45.0%)	82(55.0%)	
Blood loss (mL)				0.930			0.116			0.653
≥200	110	55(50.0%)	55(50.0%)		60(54.5%)	50(45.5%)		51(46.4%)	59(53.6%)	
<200	77	39(50.6%)	38(49.4%)		33(42.9%)	44(57.1%)		33(42.9%)	44(57.1%)	

(*Continued*)

Table 4 (Continued).

Variable	Case	SII < 371.6	SII ≥ 371.6	P	PNI < 44.0	PNI ≥ 44.0	P	AAR < 1.0	AAR ≥ 1.0	P
Complication				0.720			0.313			0.474
Yes	178	90(50.6%)	88(49.4%)		90(50.6%)	88(49.4%)		81(45.5%)	97(54.5%)	
No	9	4(44.4%)	5(55.6%)		3(33.3%)	6(66.6%)		3(33.3%)	6(66.6%)	

Abbreviations: BMI, Body Mass Index; SII, Systemic Immune-Inflammation Index; PNI, prognostic nutritional index; SIRI, Systemic Inflammation Response Index; PLR, platelet-to-lymphocyte ratio; GLR, gamma-glutamyl transpeptidase-to-lymphocyte ratio; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; AAR, aspartate aminotransferase-to-alanine aminotransferase ratio.

groups ($P > 0.05$). In contrast, patients with low PNI had significantly shorter OS compared to those with high PNI ($P < 0.05$; Figure 1D), while DFS remained comparable between the two groups ($P > 0.05$).

The Prognostic Value of SII Combined with AAR and PNI for HCC After Hepatectomy

To evaluate the prognostic value of the combined use of SII, AAR, and PNI for survival in patients with HCC, a scoring system was established by integrating these three biomarkers. Patients with SII < 371.6, AAR < 1.0, and PNI ≥ 44.0 were assigned a score of 0 and categorized into Group 1. Patients with one or two abnormal values—specifically, SII ≥ 371.6, AAR ≥ 1.0, or PNI < 44.0—were assigned a score of 1 and classified as Group 2. Patients with all three abnormal values (SII ≥ 371.6, AAR ≥ 1.0, and PNI < 44.0) were assigned a score of 2 and classified as Group 3. Kaplan–Meier analysis demonstrated that OS in Group 3 was significantly worse than in Groups 1 and 2 ($P < 0.05$), while no significant difference was observed between Groups 1 and 2 ($P > 0.05$). Similarly, DFS in Group 3 was significantly worse than in Group 2 ($P < 0.05$); however, no significant difference was found between Group 1 and either Group 2 or Group 3 ($P > 0.05$) (Figure 2A and B). Furthermore, Kaplan–Meier curves confirmed that postoperative OS and DFS were significantly poorer in Group 3 (score 2) compared to Groups 1 and 2 ($P < 0.05$) (Figure 2C and D). Specifically, the 1-, 3-, and 5-year OS rates were 100.0%, 45.0%, and 10.0%, respectively, in Group 1; 93.8%, 52.7%, and 17.8% in Group 2; and 71.4%, 23.8%, and 0.0% in Group 3. Similarly, the 1-, 3-, and 5-year DFS rates were 70.0%, 5.0%, and 0.0% in Group 1; 64.4%, 20.5%, and 6.2% in Group 2; and 42.9%, 0.0%, and 0.0% in Group 3.

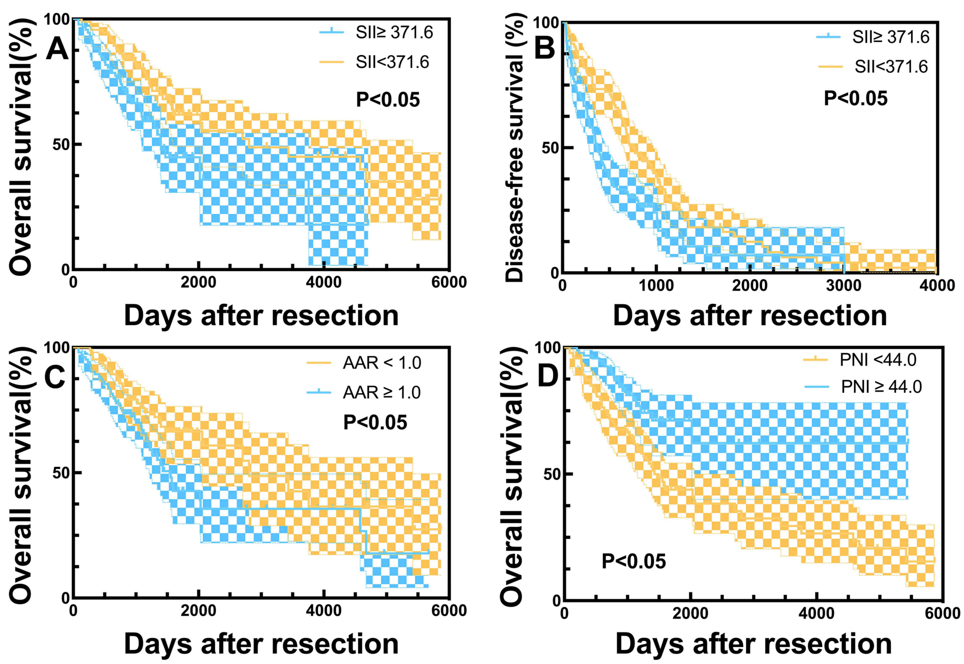

Figure 1 Kaplan–Meier curves for OS and DFS based on preoperative SII, AAR, and PNI. (**A** and **B**) SII≥371.6 was associated with significantly worse OS and DFS. (**C**) AAR≥1.0 was linked to poorer OS. (**D**) PNI<44.0 was associated with reduced OS.

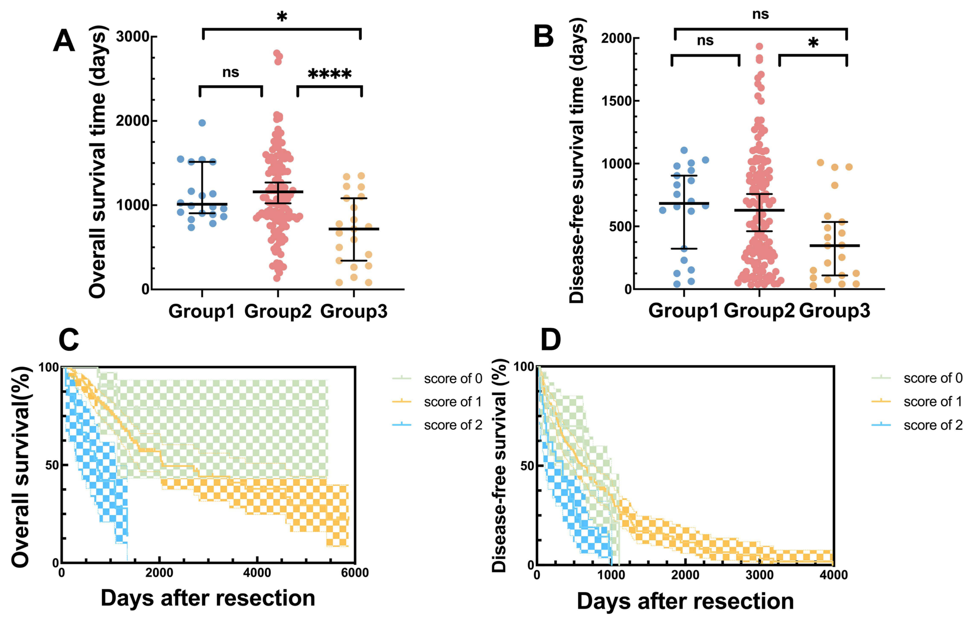

Figure 2 Prognostic significance of the combined SII, AAR, and PNI scoring system in patients with HCC. (**A** and **B**) Comparisons of OS and DFS times across the three score groups. Data are shown as mean ± SD.(**C** and **D**) Kaplan–Meier curves for OS and DFS according to score groups. **P* < 0.05, *****P* < 0.0001, ns: not significant.

Prognostic Nomograms for OS and DFS

Based on the multivariate Cox regression results, nomograms were generated to visually illustrate the relative contribution of each independent prognostic factor to OS and DFS at 1, 3, and 5 years (Figure 3A and B). Variables that were statistically significant in the multivariate analysis, along with clinically relevant factors, were incorporated into the models. Each prognostic variable corresponds to a specific number of points, which can be determined by drawing a vertical line upward to the points scale. The total score, calculated by summing the individual points, is then projected downward to estimate the probability of survival at the specified time points. The graphical display allows an intuitive understanding of how the combined effects of these biomarkers and clinical variables relate to survival outcomes.

Discussion

Surgical resection remains the most effective curative treatment for patients with resectable hepatocellular carcinoma (HCC). However, the high postoperative recurrence rate severely limits long-term survival, with up to 70% of patients experiencing relapse and nearly half succumbing within five years after surgery.[17–19] Therefore, identifying reliable preoperative prognostic biomarkers is crucial for improving postoperative management and individualized treatment strategies.

Our study demonstrated that elevated SII and AAR, along with decreased PNI, were independently associated with worse OS in HCC patients following curative hepatectomy. Additionally, SIRI emerged as an independent predictor of DFS. By integrating these markers, we developed a composite prognostic score that effectively stratified patients according to risk, with those harboring all three adverse biomarker abnormalities exhibiting significantly poorer OS and DFS. To facilitate clinical application, nomograms incorporating these biomarkers and key clinical variables were constructed to provide individualized survival predictions.

SII reflects the interplay between host inflammatory response and immune competence, incorporating neutrophil, platelet, and lymphocyte counts. Elevated SII, characterized by increased neutrophils and platelets alongside decreased lymphocytes, may promote tumor progression through fostering a pro-tumor inflammatory microenvironment, enhancing angiogenesis, and enabling immune evasion.[20] Consistent with previous reports,[21,22] our results confirm SII as a robust independent predictor of both OS and DFS in HCC. Moreover, a high SII was significantly correlated with liver cirrhosis, hypertension, elevated SIRI, and larger tumor size, highlighting its relationship with aggressive tumor biology and impaired liver function.

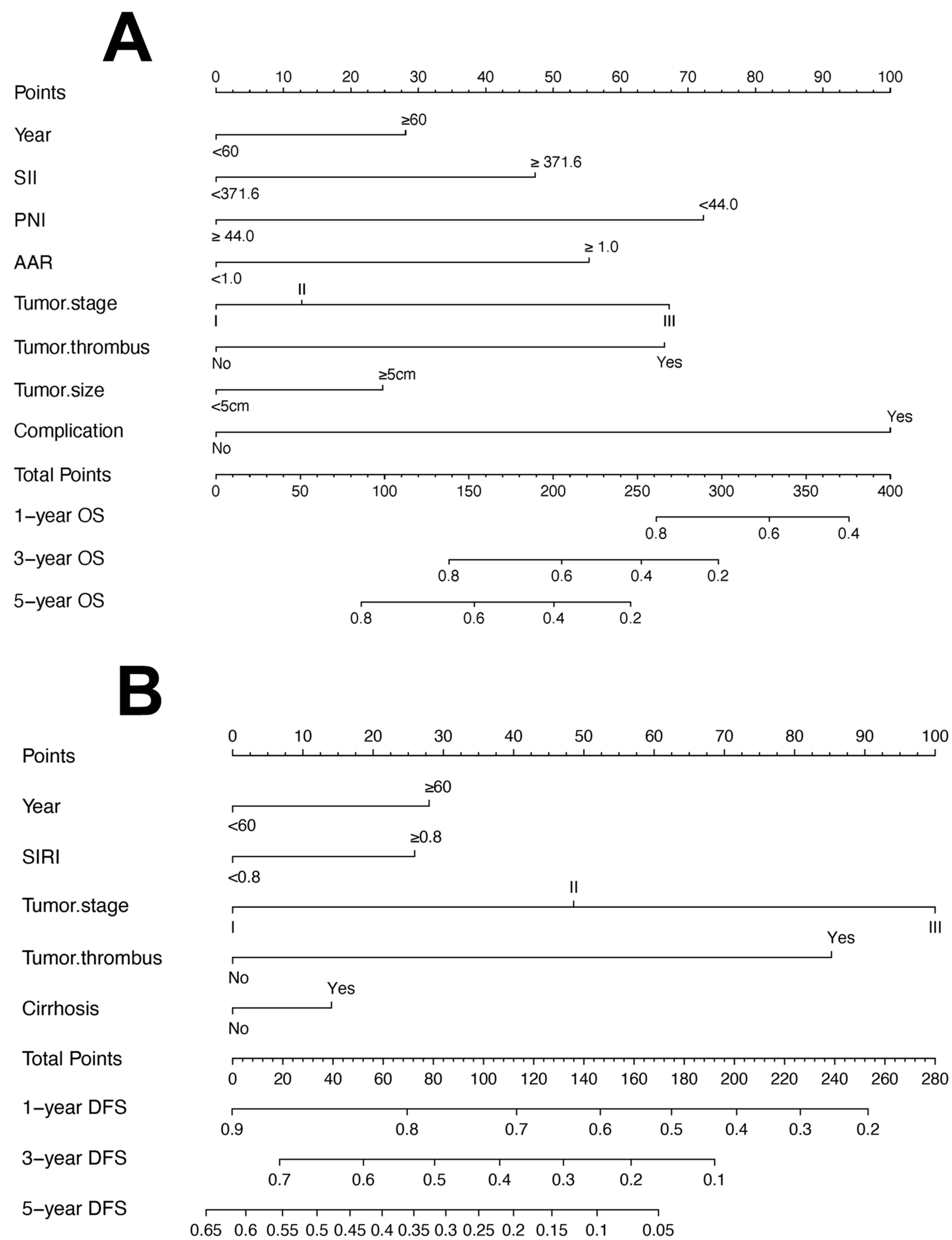

Figure 3 Nomograms predicting 1-, 3-, and 5-year survival in HCC patients. (**A**) OS model including SII, PNI, AAR, tumor stage, tumor thrombus, tumor size, complications, and age. (**B**) DFS model including SIRI, tumor stage, tumor thrombus, cirrhosis, and age. Total points are calculated by summing the scores of each variable to estimate survival probabilities.

PNI, calculated from serum albumin levels and lymphocyte count, reflects the patient's nutritional and immunological status. Low PNI has been linked to malnutrition and compromised immune surveillance, which may facilitate tumor aggressiveness and metastasis.[23,24] In our cohort, low PNI independently predicted poorer OS but not DFS, differing somewhat from prior studies,[25] possibly due to differences in patient staging and treatment modalities. Notably, low PNI was associated with unfavorable clinicopathological features, including higher BMI, larger and multiple tumors, and elevated GLR and GPR levels, underscoring the multifaceted impact of nutritional status on HCC progression.

The AAR, as a surrogate marker for chronic liver injury and fibrosis, has important prognostic value for the development and progression of hepatocellular carcinoma.[26–29] In our study, AAR demonstrated significant prognostic value for OS, whereas it did not independently predict DFS. Elevated AAR likely reflects impaired hepatic functional reserve rather than intrinsic tumor aggressiveness or recurrence risk. Patients with elevated AAR are more prone to hepatic decompensation or liver failure, which exert a pronounced impact on OS, whereas DFS is mainly determined by tumor-related factors such as stage, vascular invasion, and tumor burden.[30,31] Therefore, these findings suggest that AAR has greater prognostic relevance for OS than for DFS, underscoring the critical role of hepatic functional reserve in shaping long-term outcomes.

Among the inflammatory and fibrosis markers examined, SII, PNI, and AAR were significant for OS, while only SIRI and tumor thrombus independently predicted DFS, underscoring the importance of perioperative tumor burden and baseline systemic inflammatory status in tumor recurrence. The identification of SIRI as a prognostic factor highlights the potential role of sustained inflammation in promoting relapse through immune cell overactivation and tumor microenvironment remodeling.[32,33] Overall, these findings reflect the distinct biological underpinnings of recurrence versus overall mortality.

By jointly evaluating SII, AAR, and PNI, we were able to capture multiple dimensions of patient status—systemic inflammation, nutritional and immune competence, and liver injury—which were strongly associated with survival outcomes. Patients presenting with all three unfavorable markers experienced markedly reduced 1-, 3-, and 5-year OS and DFS rates, underscoring the clinical relevance of assessing these biomarkers in combination. These findings are consistent with previous reports highlighting the prognostic importance of inflammation and fibrosis markers in HCC.[34–36] Although we applied a simplified grouping approach without statistical weighting, this stratification method demonstrated clear survival separation and may aid in identifying high-risk patients preoperatively. In addition, nomograms were generated based on the multivariate Cox analysis to provide a graphical representation of the relative contributions of these biomarkers and other clinical variables to OS and DFS at 1, 3, and 5 years.

Certainly, the present study has some limitations. First, it was a retrospective, single-center study with a relatively small sample size, which may limit the generalizability of the findings. Second, inflammatory and nutritional markers could have been influenced by unmeasured confounding factors. Third, the composite score was simplified and not statistically weighted. A further limitation is that the nomograms were not externally validated, which restricts the generalizability of our findings. Future studies should focus on validating these models in larger, prospective, multicenter cohorts to confirm their robustness and clinical utility.

In conclusion, preoperative inflammatory and liver fibrosis markers, including SII, AAR, PNI, and SIRI, were significantly associated with the prognosis of HCC patients undergoing curative hepatectomy. These markers provide valuable prognostic information and may contribute to survival prediction. Nomograms integrating these variables demonstrated encouraging predictive performance, but their clinical utility requires validation in larger, prospective, multicenter cohorts.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Zhejiang Cancer Hospital [Approval No. IRB-2025-337(IIT)]. The requirement for informed consent was waived due to the retrospective nature of the study and anonymized data analysis.

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Author Contributions

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

Consent for Publication

This study was a retrospective analysis of anonymized patient data. No identifiable personal information is included in this manuscript, and therefore individual consent for publication was waived by the institutional ethics committee.

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Disclosure

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

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