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ORIGINAL RESEARCH

Preoperative SII Can Predict Postoperative Recurrence and Serious Complications in Patients with Hepatolithiasis

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Purpose: The occurrence and progression of hepatolithiasis are related to inflammatory reactions and immune proteins. This study aims to evaluate the relationship between systemic immune index (SII) in recurrence-free survival (RFS), as well as the incidence of severe postoperative complications in hepatolithiasis patients.

Patients and Methods: We retrospectively analyzed 177 patients with hepatolithiasis. The optimal cut-off values of SII, systemic inflammatory response index (SIRI), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR) and prognostic nutritional index (PNI) were evaluated by the analysis of the receiver operating characteristic (ROC) curve. The relationship between SII, SIRI, NLR and clinical results was tested with χ^2-test. Logical regression analysis is used to evaluate the risk factors of postoperative serious complications. The Kaplan-Meier survival curve and Cox regression analyses are used to evaluate the impact of SII, SIRI, NLR on RFS.

Results: The analysis of the ROC curve determines the optimal cut-off value and the area under the curve (AUC) of SII, SIRI, NLR, MLR, PLR and PNI, and then grouped. In the multivariate analysis, surgical method (HR=3.331, 95% CI: 1.360–8.158, p=0.008) and SII (HR=2.883, 95% CI: 1.084–7.668, p=0.034) were identified as independent risk factors for serious postoperative complications; the multivariate cox regression analysis demonstrated that a history of gallstones (HR=1.965, 95% CI: 1.206–3.201, p=0.007), SII (HR=2.818, 95% CI: 1.340–5.926, p=0.006), and MLR (HR=3.240, 95% CI: 1.158–9.067, p=0.025) were independent risk factors for RFS; survival analysis results show that patients with low levels of SII (p<0.001), SIRI (p=0.005), and NLR (p<0.001) had significantly higher RFS compared to those in the high-level group.

Conclusion: Preoperative high levels of SII, SIRI, and NLR are associated with postoperative recurrence in patients with hepatolithiasis, with SII identified as an independent risk factor for both postoperative RFS and serious complications.

Keywords: hepatolithiasis, systemic immune index, systemic inflammatory response index, recurrence-free survival, postoperative complications, predict

Introduction

Hepatolithiasis is a common disease in Southeast Asia, particularly in China, Japan, South Korea, Malaysia, and other regions, with an incidence reaching 30–50%.[1] In contrast, the incidence in European and American countries was about 0.6–1.3% in the past, though it has gradually increased in recent years.[2] The primary clinical manifestations of hepatolithiasis include abdominal pain, jaundice, fever, and related symptoms. Over time, the disease may progress to

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cirrhosis, liver atrophy, or even intrahepatic bile duct cancer.[3,4] In such cases, hepatectomy is regarded as the optimal treatment for liver stones, as it allows for the removal of both stones and liver lesions simultaneously.[5,6]

The exact cause of hepatolithiasis remains unclear, but factors such as cholestasis, infection, metabolic changes, and malnutrition are thought to be involved.[7] Moreover, research has demonstrated that inflammatory responses and immune proteins play a significant role in the occurrence and progression of hepatolithiasis.[8,9] Several inflammatory and nutritional indicators have been emphasized in predicting patients' postoperative outcomes, including the prognostic nutritional index (PNI), platelet/lymphocyte ratio (PLR), lymphocyte/neutrophil ratio (NLR), and monocyte/lymphocyte ratio (MLR).[10–13] However, each of these indicators focuses on only two types of immune cells.

Recently, the systemic immune index (SII) and systemic inflammatory response index (SIRI) have been recognized as more comprehensive inflammatory and immune biomarkers. These indices incorporate changes in multiple cell types, providing a more accurate reflection of the body's current inflammatory and immune status. Numerous studies have highlighted the significant role of inflammatory and nutritional indices in predicting postoperative recurrence and prognosis in various diseases, including bladder cancer, hip fractures, aortic dissection, and hepatocellular carcinoma.[14–17] Nevertheless, no literature has yet reported on the predictive value of these indices in patients with hepatolithiasis.

The aim of this study is to systematically evaluate the association between recurrence-free survival (RFS) and serious complications in relation to SII in patients with hepatolithiasis, reflecting both long-term and short-term clinical outcomes, respectively. Additionally, we analyzed the correlation between NLR, SIRI, and postoperative recurrence, as well as serious complications.

Materials and Methods

This is a retrospective cohort study conducted at a tertiary medical center, adhering to the ethical principles of the Helsinki Declaration (revised in 2013). The study was approved by the Institutional Review Committee (Ethics Review Number: LYLL (2024) KY 166). Due to the retrospective design of the study, informed consent was waived, and all patient data were anonymized and de-identified.

Study Population

This study included 177 patients with hepatolithiasis who underwent hepatectomy at our center between January 2017 and September 2023. The inclusion criteria were: (1) age ≥18 years; (2) diagnosis of hepatolithiasis confirmed by preoperative imaging; and (3) complete clinical and follow-up data. The exclusion criteria were: (1) postoperative pathology indicating coexistent liver cancer; (2) diseases affecting inflammatory indices, such as malignancies, autoimmune diseases, or hematologic disorders; (3) prior hepatectomy or biliary-enteric anastomosis; and (4) incomplete clinical data or loss to follow-up. The flowchart is shown in Figure 1.

Data Collection and Definition

The variables collected in this study include: gender, age, body mass index (BMI), hypertension, diabetes, history of gallstones, Stone distribution, Charlson comorbidity index (CCI), Child-Pugh grade, American Society of Anesthesiologists (ASA) score, white blood cell count (WBC), platelet count (PLT), hemoglobin (Hb), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI), prognostic nutritional index (PNI), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), albumin (ALB), prothrombin time (PT), international normalized ratio (INR), T-tube drainage, biliary exploration, surgical method, type of resection, perioperative blood transfusion, history of gallstones, and postoperative complications.

NLR was calculated as neutrophil count/lymphocyte count, MLR as monocyte count/lymphocyte count, PLR as platelet count/lymphocyte count, SII as platelet count * NLR, and SIRI as monocyte count * NLR. PNI was calculated as albumin + 5 * total lymphocyte count.

The variables were dichotomized based on clinically significant thresholds: age (60 years), BMI (25 kg/m^2), WBC (10×10^9/L), Hb (110 g/L), TBIL (17.1 μmol/L), ALT (40 U/L), AST (40 U/L), ALB (35 g/L), PT (13.5 s), and PLT (100×10^3/μL).

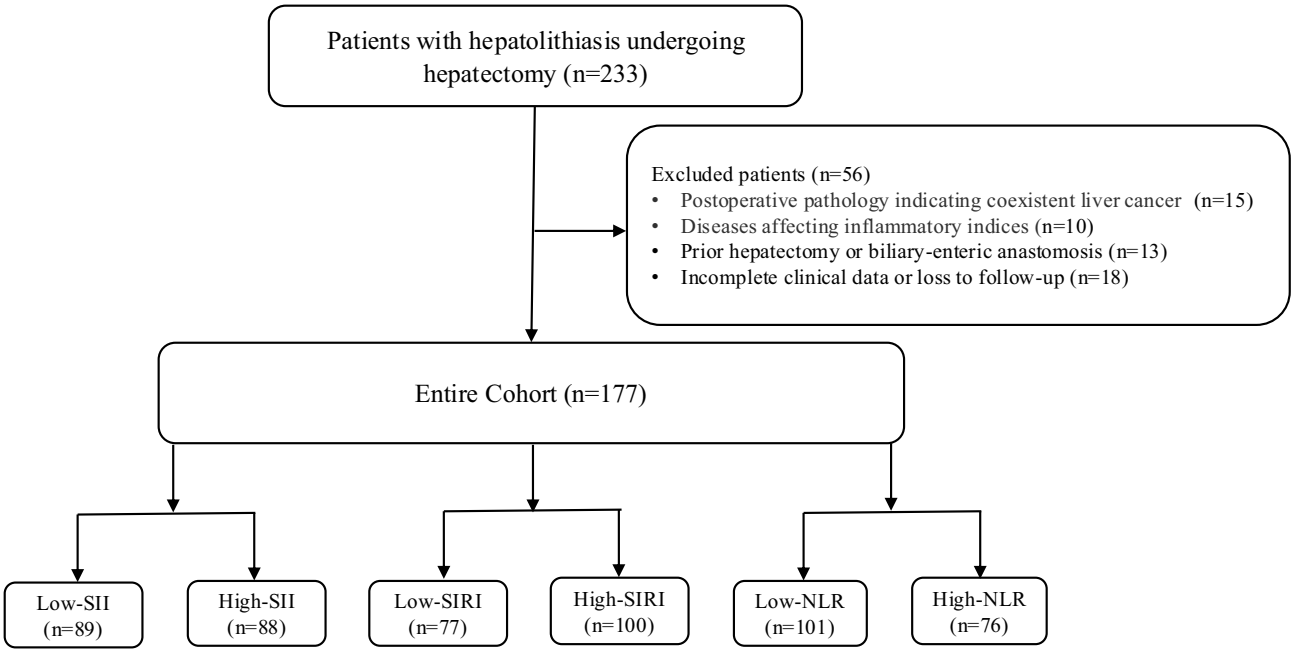

Figure 1 Patient Selection Flowchart.
Abbreviations: SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NLR, neutrophil/lymphocyte ratio.

Postoperative complications primarily included lung infection, pleural effusion, liver failure, infection, bleeding, thrombosis, bile leakage, ascites, and gastric paralysis, which were classified according to the Clavien-Dindo classification.[18] Serious complications were defined as Clavien-Dindo grade ≥IIIa.

Follow-Up

All patients underwent computed tomography (CT) and T-tube cholangiography before discharge to check for residual stones. After discharge, ultrasound or CT scans were conducted every 3–6 months to monitor for the recurrence of intrahepatic or extrahepatic stones. The final follow-up was conducted in August 2024.

Statistical Analysis

SPSS (V26.0) software was used for statistical analysis. The normality of the distribution was assessed using the Shapiro–Wilks test. Continuous variables with a normal distribution are expressed as the mean [SD], while those with a non-normal distribution are presented as the median [interquartile range (IQR)]. Categorical variables are expressed as counts (percentage). The independent sample *t* test or Mann–Whitney *U*-test was employed to compare continuous variables, while the χ^2-test or Fisher's exact test was used for categorical data. The accuracy of SII, SIRI, NLR, MLR, PLR, and PNI in predicting RFS was assessed using receiver operating characteristic (ROC) analysis. The results are reported as the area under the curve (AUC), with the optimal cut-off points, sensitivity, and specificity noted. The cut-off value corresponding to the maximum value of the Youden index was selected as the best cut-off, and patients were divided into high and low groups according to the optimized cut-off for each index. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship between each index and serious complications. The Kaplan-Meier method was used to construct survival curves, and the Log rank test was applied to compare differences between the two groups. Additionally, the univariate Cox proportional hazards model was used to estimate the impact of each predictor on RFS. A multivariate Cox proportional hazards model was conducted to account for potential confounding factors and to identify independent predictors of RFS. All p values <0.05 were considered statistically significant.

Results

Patient Characteristics

This study included 177 patients, with 54 (30.5%) males and 123 (69.5%) females, with an average age of 58.07 ± 11.59 years and a BMI of 26.27 (23.94, 28.34) kg/m^2. A total of 117 (66.1%) patients underwent laparoscopic hepatectomy, while 17 (9.6%) patients underwent anatomical resection. As of August 31, 2024, the median follow-up period for all patients was 30.63 months, during which 70 (39.5%) patients experienced recurrence of intrahepatic and extrahepatic stones.

Optimal Cutoff Value for SII, SIRI, NLR, MLR, PLR and PNI

Receiver operating characteristic (ROC) curve analysis was used to predict RFS, and the maximum Youden index, calculated as "sensitivity + specificity - 1", was used to determine the best cutoff values for each index. The optimal cutoff values for SII, SIRI, NLR, MLR, PLR, and PNI were 553.68, 0.79, 3.13, 0.16, 210.53, and 51.08, respectively. The detailed results are shown in Figure 2 and Table 1.

Based on predictive accuracy, the top three indices, SII, SIRI, and NLR, were selected for further grouping and analysis. The results are presented in Table 2. In the SII group, significant differences were observed in WBC (p<0.001), Hb (p=0.042), ALT (p<0.001), AST (p=0.008), TBIL (p<0.001), ALB (p=0.002), MLR (p<0.001), PLR (p<0.001), perioperative blood transfusion (p=0.020), serious complications (p=0.008), and recurrence (p<0.001). In the SIRI group, significant differences were found in gender (p=0.002), WBC (p<0.001), ALT (p=0.016), AST (p=0.003), TBIL (p<0.001), ALB (p=0.031), PNI (p=0.006), MLR (p<0.001), PLR (p<0.001), and recurrence (p=0.001). In the NLR group, significant differences were noted in gender (p=0.010), history of gallstones (p=0.042), WBC (p<0.001), AST

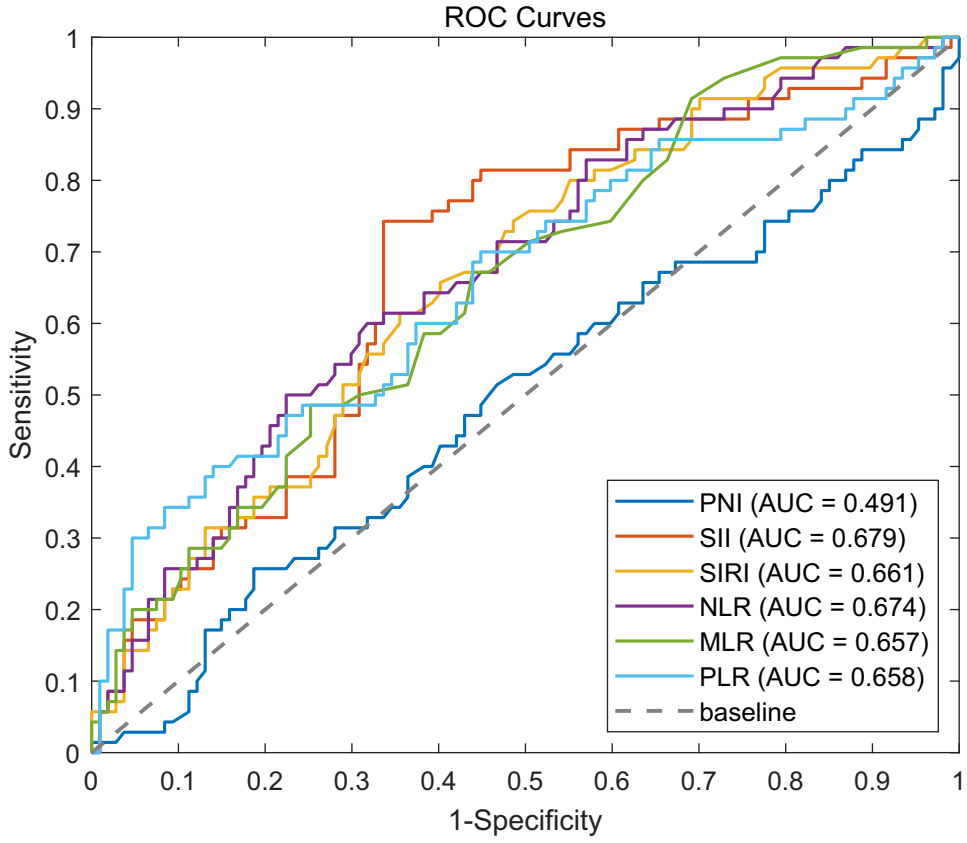

Figure 2 The receiver operation characteristic (ROC) curve is used to compare the predictive ability of several preoperative indices.
Abbreviations: PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Table 1 Optimal Cutoff Value for SII, SIRI, NLR, MLR, PLR and PNI

Variable	Cut-off	P value	AUC	Youden Index
SII	553.684	<0.001	0.679	0.407
NLR	3.132	<0.001	0.674	0.292
SIRI	0.789	<0.001	0.661	0.262
PLR	210.527	<0.001	0.658	0.260
MLR	0.164	<0.001	0.657	0.237
PNI	51.075	0.832	0.491	0.070

Abbreviations: AUC, area under the curve; SII, systemic immune-inflammation index; NLR, neutrophil/lymphocyte ratio; SIRI, systemic inflammatory response index; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PNI, prognostic nutritional index.

Table 2 The Relationship Between SII, SIRI, NLR and Clinical Outcomes in Patients With Hepatolithiasis

Variables (n, %)	SII			SIRI			NLR		
	Low (n=89)	High (n=88)	P	Low (n=77)	High (n=100)	P	Low (n=101)	Hight (n=76)	P
Sex, male	23(25.8)	31(35.2)	0.175	14(18.2)	40(40.0)	0.002	23(22.8)	31(40.8)	0.010
Age < 60 y	54(60.7)	54(61.4)	0.925	24(31.2)	45(45.0)	0.061	67(66.3)	41(53.9)	0.094
BMI < 25 kg/m^2	60(67.4)	51(58.0)	0.193	52(67.5)	59(59.0)	0.245	66(65.3)	45(59.2)	0.403
Hypertension	17(19.1)	9(10.2)	0.095	11(14.3)	15(15.0)	0.894	16(15.8)	10(13.2)	0.618
Diabetes	8(9.0)	4(4.5)	0.240	6(7.8)	6(6.0)	0.638	8(7.9)	4(5.3)	0.486
History of gallstones	30(33.7)	32(36.4)	0.711	24(31.2)	38(38.0)	0.345	29(28.7)	33(43.4)	0.042
ASA score			0.477			0.459			0.454
1	1(1.1)	0(0)		1(1.3)	0(0)		1(1.0)	0(0)	
2	79(88.8)	76(86.4)		68(88.3)	87(87.0)		90(89.1)	65(85.5)	
3	9(10.1)	12(13.6)		8(10.4)	13(13.0)		10(9.9)	11(14.5)	
CCI score < 4	64(71.9)	61(69.3)	0.705	54(70.1)	71(71.0)	0.900	70(69.3)	55(72.4)	0.658
Child-Pugh grade			0.056			0.055			0.052
A	85(95.5)	77(87.5)		74(96.1)	88(88.0)		96(95.0)	5(5.0)	
B	4(4.5)	11(12.5)		3(3.9)	12(12.0)		66(86.8)	10(13.2)	
WBC ≤ 10 x 10^9/L	89(100)	71(80.7)	<0.001	77(100)	83(83.0)	<0.001	100(99.0)	60(78.9)	<0.001
PLT < 100 x 10^3/uL	8(9.0)	3(3.4)	0.124	6(7.8)	5(5.0)	0.446	6(5.9)	5(6.6)	0.862
Hb < 110 g/L	10(11.2)	20(22.7)	0.042	11(14.3)	19(19.0)	0.407	14(13.9)	16(21.1)	0.207
ALT ≤ 40 U/L	69(77.5)	47(53.4)	<0.001	58(75.3)	58(58.0)	0.016	72(71.3)	44(57.9)	0.063
AST ≤ 40 U/L	74(83.1)	58(65.9)	0.008	66(85.7)	66(66.0)	0.003	82(81.2)	50(65.8)	0.020
TBIL ≤ 17.1 umol/L	78(87.6)	58(65.9)	<0.001	69(89.6)	67(67.0)	<0.001	91(90.1)	45(59.2)	<0.001
ALB ≤ 35g/dL	13(14.6)	31(35.2)	0.002	13(16.9)	31(31.0)	0.031	20(19.8)	24(31.6)	0.073
PT ≤ 13.5 s	77(86.5)	70(79.5)	0.216	67(87.0)	80(80.0)	0.218	88(87.1)	59(77.6)	0.096
PNI ≤ 50.08	65(73.0)	74(84.1)	0.073	53(68.8)	86(86.0)	0.006	72(71.3)	67(88.2)	0.007
MLR ≤ 0.16	27(30.3)	7(8.0)	<0.001	30(39.0)	4(4.0)	<0.001	31(30.7)	3(3.9)	<0.001
PLR ≤ 210.53	87(97.8)	47(53.4)	<0.001	71(92.2)	63(63.0)	<0.001	91(90.1)	43(56.6)	<0.001
Stone distribution			0.894			0.516			0.919
Left hepatic	60(67.4)	61(69.3)		50(64.9)	71(71.0)		68(67.3)	53(69.7)	
Right hepatic	10(11.2)	8(9.1)		10(13.0)	8(8.0)		11(10.9)	7(9.2)	
Bilatera hepatic	19(21.4)	2(1.6)		17(22.1)	21(21.0)		22(21.8)	16(21.1)	
Surgical method			0.561			0.725			0.939
Open	32(36.0)	28(31.8)		25(32.5)	35(35.0)		34(33.7)	67(66.3)	

(*Continued*)

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Table 2 (Continued).

Variables (n, %)	SII			SIRI			NLR		
	Low (n=89)	High (n=88)	P	Low (n=77)	High (n=100)	P	Low (n=101)	Hight (n=76)	P
Laparoscopy	57(64.0)	60(68.2)		52(67.5)	65(65.0)		26(32.2)	50(65.8)	
Anatomical resection	12(13.5)	5(5.7)	0.078	9(11.7)	8(8.0)	0.409	14(13.9)	3(3.9)	0.027
T-tube drainage	37(41.6)	43(48.9)	0.330	31(40.3)	49(49.0)	0.247	40(39.6)	40(52.6)	0.085
Biliary exploration	71(79.8)	68(77.3)	0.685	58(75.3)	81(81.0)	0.362	79(78.2)	60(78.9)	0.907
Perioperative blood transfusion	26(29.2)	13(14.8)	0.020	22(28.6)	17(17.0)	0.066	27(26.7)	12(15.8)	0.082
Clacien Dindo ≥ IIIa	8(9.0)	21(23.9)	0.008	9(11.7)	20(20.0)	0.139	14(13.9)	15(19.7)	0.296
30-day readmission	2(2.2)	3(3.4)	0.641	3(3.9)	2(2.0)	0.450	3(3.0)	2(2.6)	0.893

Abbreviations: SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NLR, neutrophil/lymphocyte ratio; BMI, body mass index; ASA, American Society of Anesthesiologists; CCI, charlson comorbidity index; WBC, white blood cell count; PLT, platelet count; Hb, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PNI, prognostic nutritional index; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

(p=0.020), TBIL (p<0.001), PNI (p=0.007), MLR (p<0.001), PLR (p<0.001), anatomical resection (p=0.027), and recurrence (p<0.001).

Univariate and Multivariate Logistic Regression Analysis on the Occurrence of Serious Complications

For serious complications, we primarily recorded cases classified as Clavien-Dindo ≥ IIIa, which included issues such as bleeding, bile leakage, pulmonary embolism, shock, infection, and thoracic or peritoneal effusions that required re-operation. The results of the univariate and multivariate logistic regression analyses are shown in Table 3. In the univariate analysis,

Table 3 Univariate and Multivariate Logistic Regression Analysis on the Occurrence of Serious Postoperative Complications

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (Female vs Male)	0.971(0.410–2.297)	0.946		
Hypertension (Yes vs No)	1.670(0.605–4.605)	0.318		
Diabetes (Yes vs No)	0.445(0.055–3.586)	0.435		
History of gallstones (Yes vs No)	2.302(1.028–5.157)	0.039	1.684(0.695–4.081)	0.249
Age, y (≤60 vs >60)	2.206(0.986–4.936)	0.051		
BMI, kg/m^2 (<25 vs ≥25)	1.229(0.546–2.766)	0.618		
CCI score (<4 vs ≥5)	2.271(1.002–5.146)	0.046	2.215(0.903–5.435)	0.082
Child-Pugh grade (A vs B)	2.875(0.903–9.150)	0.064		
T-tube drainage (Yes vs No)	0.982(0.441–2.187)	0.965		
Surgical method (Laparoscopy vs Open)	3.459(1.524–7.852)	0.002	3.331(1.360–8.158)	0.008
Anatomical resection (Yes vs No)	1.104(0.296–4.117)	0.882		
ASA score (≤2 vs >3)	1.233(0.383–3.973)	0.726		
Biliary exploration (Yes vs No)	1.377(0.488–3.891)	0.544		
Perioperative blood transfusion (Yes vs No)	1.438(0.581–3.556)	0.43		
WBC, x 10^9/L (≤10 vs >10)	1.104(0.269–4.117)	0.882		
Hb, g/L (<110 vs ≥110)	1.934(0.545–6.857)	0.3		
PLT, x 10^3/uL (<100 vs ≥100)	2.029(0.250–16.493)	0.5		
ALT, U/L (≤40 vs >40)	1.693(0.754–3.800)	0.199		

(*Continued*)

Table 3 (Continued).

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
AST, U/L (≤40 vs >40)	1.143(0.467–2.798)	0.77		
TBIL, umol/L (≤17.1 vs >17.1)	2.404(1.027–5.626)	0.039	1.634(0.624–4.278)	0.317
ALB, g/dL (≤35 vs >35)	0.391(0.169–0.902)	0.024	0.579(0.231–1.449)	0.243
PT, s (≤13.5 vs >13.5)	1.025(0.357–2.944)	0.963		
PNI (≤50.08 vs >50.08)	0.726(0.257–2.051)	0.544		
SII (≤533.68 vs >533.68)	3.174(1.321–7.623)	0.008	2.883(1.084–7.668)	0.034
SIRI (≤0.79 vs >0.79)	1.889(0.807_4.442)	0.139		
NLR (≤3.13 vs >3.13)	1.528(0.688–3.369)	0.296		
MLR (≤0.16 vs >0.16)	0.701(0.272–1.809)	0.461		
PLR (≤210.53 vs >210.53)	1.230(0.501–3.020)	0.651		

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; CCI, charlson comorbidity index; WBC, white blood cell count; PLT, platelet count; Hb, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

history of gallstones, CCI, surgical methods, TBIL, ALB, and SII were identified as significant risk factors for serious postoperative complications. In the multivariate analysis, surgical method (HR=3.331, 95% CI: 1.360–8.158, p=0.008) and SII (HR=2.883, 95% CI: 1.084–7.668, p=0.034) were identified as independent risk factors for serious postoperative complications.

Association of SII, SIRI, and NLR with Recurrence-Free Survival

We compared the relationship between SII, SIRI, and NLR with long-term outcomes. As illustrated in Figure 3, the analysis revealed that patients with low levels of SII (p<0.001), SIRI (p=0.005), and NLR (p<0.001) had significantly higher RFS compared to those in the high-level group.

Univariate and Multivariate Cox Regression Analyses for Recurrence-Free Survival

The univariate analysis indicated that a history of gallstones, SII, SIRI, NLR, MLR, and PLR are significant prognostic factors associated with RFS. Multivariate Cox regression analysis demonstrated that a history of gallstones (HR=1.965, 95% CI: 1.206–3.201, p=0.007), SII (HR=2.818, 95% CI: 1.340–5.926, p=0.006), and MLR (HR=3.240, 95% CI: 1.158–9.067, p=0.025) were independent risk factors for RFS. In contrast, SIRI, NLR, and PLR were not identified as independent risk factors for RFS, as shown in Table 4.

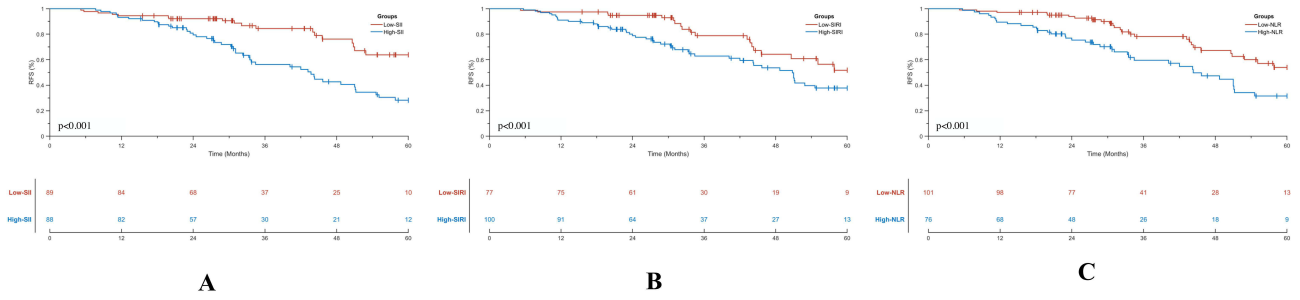

Figure 3 Kaplan-Meier analysis compares RFS in different groups. (**A**) Kaplan-Meier analysis compared the RFS of two groups of SII; (**B**) Kaplan-Meier analysis compared the RFS of two groups of SIRI; (**C**) Kaplan-Meier analysis compared the RFS of two groups of NLR.
Abbreviations: RFS, recurrence-free survival; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NLR, neutrophil/lymphocyte ratio.

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Table 4 Univariate and Multivariate Cox Regression Analyses for Recurrence-Free Survival in Patients With Hepatolithiasis

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (Female vs Male)	0.822(0.491–1.374)	0.454		
Hypertension (Yes vs No)	0.949(0.471–1.911)	0.883		
Diabetes (Yes vs No)	0.941(0.342–2.585)	0.906		
History of gallstones (Yes vs No)	2.194(1.371–3.511)	0.001	1.965(1.206–3.201)	0.007
Age, y (≤60 vs >60)	0.987(0.609–1.600)	0.958		
BMI, kg/m^2 (<25 vs ≥25)	1.358(0.845–2.183)	0.206		
CCI score (<4 vs ≥5)	0.925(0.550–1.555)	0.768		
Child-Pugh grade (A vs B)	1.069(0.489–2.338)	0.867		
T-tube drainage (Yes vs No)	1.062(0.664–1.700)	0.801		
Surgical method (Laparoscopy vs Open)	0.730(0.447–1.192)	0.208		
Anatomical resection (Yes vs No)	0.930(0.425–2.036)	0.855		
ASA score (≤2 vs >3)	1.089(0.555–2.138)	0.804		
Biliary exploration (Yes vs No)	0.752(0.412–1.371)	0.352		
Perioperative blood transfusion (Yes vs No)	0.566(0.289–1.108)	0.097		
WBC, x 10^9/L (≤10 vs >10)	1.145(0.546–2.398)	0.72		
Hb, g/L (<110 vs ≥110)	0.602(0.344–1.053)	0.075		
PLT, x 10^3/uL (<100 vs ≥100)	0.701(0.303–1.622)	0.407		
ALT, U/L (≤40 vs >40)	1.340(0.830–2.164)	0.232		
AST, U/L (≤40 vs >40)	0.965(0.569–1.638)	0.896		
TBIL, umol/L (≤17.1 vs >17.1)	1.164(0.692–1.960)	0.567		
ALB, g/dL (≤35 vs >35)	0.899(0.523–1.547)	0.702		
PT, s (≤13.5 vs >13.5)	1.052(0.583–1.897)	0.866		
PNI (≤50.08 vs >50.08)	1.149(0.671–1.967)	0.612		
SII (≤533.68 vs >533.68)	3.233(1.891–5.530)	<0.001	2.818(1.340–5.926)	0.006
SIRI (≤0.79 vs >0.79)	2.067(1.230–3.474)	0.006	0.878(0.418–1.841)	0.73
NLR (≤3.13 vs >3.13)	2.339(1.449–3.775)	<0.001	0.864(0.413–1.808)	0.698
MLR (≤0.16 vs >0.16)	4.091(1.488–11.252)	0.006	3.240(1.158–9.067)	0.025
PLR (≤210.53 vs >210.53)	2.440(1.510–3.941)	<0.001	1.401(0.827–2.375)	0.21
Clacien Dindo (<IIIa vs ≥IIIa)	1.096(0.618–1.943)	0.754		
30-day readmission (Yes vs No)	1.423(0.446–4.541)	0.551		

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; CCI, charlson comorbidity index; WBC, white blood cell count; PLT, platelet count; Hb, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, albumin; PT, prothrombin time; PNI, prognostic nutritional index; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index; NLR, neutrophil/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

Discussion

In clinical practice, identifying simple and effective preoperative biochemical markers to predict adverse postoperative outcomes can aid doctors in making more informed clinical decisions. This study was designed with that goal in mind. Currently, SII, SIRI, NLR, MLR, PLR, and PNI are widely used to predict outcomes in various diseases.[19–22] Therefore, we selected these indices to evaluate their significance in hepatolithiasis. To the best of our knowledge, this is the first study to do so.

First, we used ROC analysis to determine the optimal cutoff values for SII, SIRI, NLR, MLR, PLR, and PNI, focusing on the top three indices based on AUC. The results of this study demonstrate that SII can serve as a predictive indicator for both RFS and serious postoperative complications in patients with hepatolithiasis undergoing hepatectomy. We found that a preoperative SII value of 533.68 was the most prognostic in this cohort. Elevated preoperative SII (>533.68) was associated with WBC, Hb, ALT, AST, TBIL, ALB, MLR, PLR, perioperative blood transfusion, and serious complications ($p<0.05$), indicating that SII not only correlates with multiple biochemical markers but also influences short-term postoperative outcomes. Furthermore, preoperative SIRI was significantly associated with gender, WBC, ALT, AST, TBIL, ALB, PNI, MLR, and PLR ($p<0.05$), while preoperative NLR was related to gender, history of

gallstones, WBC, AST, TBIL, PNI, MLR, PLR, and the type of resection ($p<0.05$). Regarding long-term outcomes, higher levels of SII, SIRI, and NLR were linked to increased recurrence rates. Through logistic regression and Cox regression analyses, SII was identified as an independent risk factor for both RFS and serious postoperative complications. These findings highlight the importance of SII in predicting adverse postoperative outcomes in patients with hepatolithiasis, providing valuable insight for clinical management.

The patient's preoperative elevated levels of SII, SIRI, and NLR have been linked to postoperative stone recurrence. These three indices share a common factor: neutrophil elevation or lymphocyte reduction, indicating either an increased inflammatory response or a weakened immune response. A systemic immune inflammatory response has been shown to play a role in the formation of stones in the biliary system. Studies have demonstrated that inflammatory biomarkers, such as IL-6, IL-8, and TNF-α, are associated with an increased risk of gallstone disease.[23] Furthermore, a prospective cohort study by Liu confirmed that C-reactive protein is an independent risk factor for gallstone disease.[24] Biliary tract infection and malnutrition are major causes of hepatolithiasis. From a pathophysiological standpoint, this can be explained: malnutrition weakens immune function, making patients more susceptible to biliary tract infections, which in turn stimulates neutrophil proliferation. Normally, most bilirubin in bile is bilirubin gluconate (conjugated bilirubin). However, during bacterial infection, beta-glucuronidase and phospholipase A1 are produced. Beta-glucuronidase hydrolyzes conjugated bilirubin into unconjugated bilirubin, which then binds with Ga^{2+} to form calcium bilirubinate precipitates. Meanwhile, phospholipase A1 hydrolyzes phospholipids, releasing free fatty acids that combine with Ga^{2+} to produce calcium palmitate and calcium stearate.[25,26] Additionally, during biliary tract infections, the biliary mucosa secretes large amounts of glycoprotein, which aggregates sediments to form stones.[27] Contrary to the role of neutrophils, lymphocytes primarily function to regulate and inhibit inflammatory reactions.[28] When lymphocyte levels decrease, the mucosa of the bile duct becomes rough due to the ongoing inflammatory response in the intrahepatic bile ducts, promoting stone formation. Research has also shown that platelets can mediate inflammatory responses,[29] consistent with the findings of this study. High levels of SII, representing elevated platelet counts, suggest that neutrophils, lymphocytes, and platelets interact to regulate the body's inflammatory and immune responses, ultimately influencing the recurrence of hepatolithiasis.

For serious complications, we primarily recorded cases classified as Clavien-Dindo grade ≥IIIa, which included issues such as bleeding, bile leakage, pulmonary embolism, shock, infection, and thoracic or peritoneal effusions that required re-operation. Preoperative SII and the surgical method were identified as independent risk factors for these complications. It has been previously demonstrated that the surgical approach influences postoperative complications.[30,31] In our study, the incidence of serious complications was significantly higher in the high-level SII group compared to the low-level SII group (9.0% vs 23.9%, $p=0.008$). Compared to other inflammatory markers, SII is a composite index of three critical cell types, offering a more comprehensive reflection of the body's inflammatory and immune status. An elevated SII suggests a more severe inflammatory response and immune dysregulation. When SII is elevated, surgery further activates the innate immune system, comprising neutrophils, monocytes, and complement, which can trigger a systemic inflammatory storm. This leads to the release of a large number of inflammatory mediators and cytokines into the bloodstream, negatively affecting multiple organs and contributing to various inflammatory complications. This phenomenon is comparable to the increased incidence of postoperative complications in COVID-19 patients, where inflammatory storms play a significant role.[32,33] Additionally, recent studies suggest that SII is linked to adverse surgical outcomes. In a retrospective study of 1056 patients, Parmana demonstrated that elevated SII levels are associated with adverse outcomes following on-pump coronary artery bypass surgery.[34] Xing's study found that SII is an independent risk factor for infection following hysterectomy,[35] and Zhang's research established a relationship between SII and thrombosis after gastrointestinal surgery.[36] Moreover, SII has been implicated in complications such as postoperative cerebral infarction, pneumonia, heart failure, and sepsis,[20,37–39] findings that align with the postoperative complications observed in our study.

There are several limitations to our study. First, this is a single-center retrospective study, which restricts the generalizability of the findings, and selection bias is inevitable In the future, multi-center prospective randomized controlled trials will be necessary to further validate these results. Second, the method for determining the optimal cutoff value for SII is most commonly done through ROC analysis or quartile methods, both of which are influenced by sample size and population characteristics. Currently, the ideal approach for determining this cutoff has not been established. Third, while this study explores the relationship between composite indices and disease, the results provide valuable insights, but the precise underlying mechanisms remain unclear.

Conclusion

Preoperative high levels of SII, SIRI, and NLR are associated with postoperative recurrence in patients with hepatolithiasis, with SII identified as an independent risk factor for both postoperative RFS and serious complications. These findings can help clinicians develop targeted clinical diagnosis and treatment strategies in advance, potentially improving the prognosis for patients with hepatolithiasis.

Data Sharing Statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Ethics Committee of the People's Hospital of Leshan (No. LYLL (2024) KY 166). Due to retrospective characteristics of the study, informed consent was waived. All patient data was treated with confidentiality.

Author Contributions

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

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Disclosure

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