

# Investigating effects of preoperative inflammatory biomarkers on predicting survival outcomes of peripheral intrahepatic cholangiocarcinoma after curative resection.

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## Research

**Keywords:** intrahepatic cholangiocarcinoma, inflammatory biomarker, systemic immune-inflammation index

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# Abstract

**Introduction:** Intrahepatic cholangiocarcinoma (ICC) stands as the second most common malignant tumor in liver with poor patient prognosis. Increasing evidences have shown that inflammation plays a significant role in tumor progression, angiogenesis and metastasis. However, the prognosis significance of inflammatory biomarkers on recurrence-free survival (RFS) and overall survival (OS) in peripheral ICC patients is poorly recognized.

**Methods:** Peripheral ICC patients who underwent curative hepatectomy and diagnosed pathologically were retrospectively analyzed. Inflammatory biomarkers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), were investigated.

**Results:** Receiver operating characteristic (ROC) curves showed no significance in NLR, PLR and LMR in RFS and OS, while significant results were shown on SII in both RFS ( $P=0.035$ ) and OS ( $P=0.034$ ) with areas under ROC curve as 0.63 (95%CI: 0.52-0.74) and 0.62 (95%CI: 0.51-0.72), respectively. Kaplan-Meier curves revealed statistically significant better survival data in SII-low groups on both RFS ( $P<0.001$ ) and OS ( $P<0.001$ ). The univariate and multivariate analyses revealed that higher level of SII was independently associated with both poorer RFS time and OS time. However, no significant result was shown on NLR, PLR or LMR.

**Conclusion:** SII is an effective prognostic factor for predicting the prognosis of peripheral ICC patient undergone curative hepatectomy, while NLR, PLR and LMR are not associated with clinical outcomes of these patients.

## Introduction

Intrahepatic cholangiocarcinoma (ICC) stands as the second common malignant hepatic neoplasms, however the incidence of ICC grows worldwide during past decades.<sup>1, 2</sup> Up to now, the best choice of curative treatments is surgical resection, while the treatments for unresectable ICC are very limited.<sup>3</sup> ICC usually grows aggressively without symptom in early stage, resulting in a small proportion of ICC patients who can receive surgery. Furthermore, the prognosis of resectable ICC patient still remains poor and half of them will suffer from recurrence after surgery.<sup>4</sup> ICC can be divided into two types according to the location: peripheral type and hilar type. Different mechanisms of oncogenesis and clinicopathologic characteristics were shown in two types according to multiple researches.<sup>5, 6</sup>

Increasing evidences have shown that inflammation and inflammatory biomarkers are significant factors in tumor microenvironment, thus promoting proliferation, angiogenesis and metastasis by various inflammatory cells and cytokines.<sup>7</sup> In recent years, multiple inflammatory biomarkers were investigated for predicting the prognosis of patients with various cancer, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-

inflammation index (SII). Significant results were reported in various type of cancer such as neck soft tissue sarcoma, lung cancer, renal cancer, and hepatocellular carcinoma.<sup>8-10</sup>

However, significance of these inflammatory biomarkers on prognosis of peripheral ICC patients underwent curative resection has not been fully understood. Therefore, the present study was performed for investigating the significance of various inflammatory biomarkers, including NLR, PLR, LMR and SII on patient prognosis in peripheral ICC after curative surgery.

## Methods

### Study cohort

Peripheral ICC patients underwent curative hepatectomy between January 2013 and December 2017 in Xiangya hospital, Central South University were retrospectively analyzed. Exclusion criteria were as followed: (1) pathology did not support the diagnosis of ICC; (2) recurrence of ICC; (3) received an anti-tumor therapy before resection; (4) suffering from infectious diseases before resection; (5) suffering from autoimmune diseases or immunodeficiency diseases; (6) patients who died of postoperative complications or reasons other than ICC; (7) R1 or R2 resection; (8) hilar type of ICC; (9) incomplete clinical data. The ethics committee of Xiangya Hospital of Central South University approved this study.

### Definitions and follow-up

The TNM stage of ICC was determined by the 8th [American Joint Committee on Cancer \(AJCC\) Cancer Staging Manual](#). NLR was calculated as neutrophil count ( $10^9/L$ )/lymphocyte count ( $10^9/L$ ). PLR was calculated as platelet ( $10^9/L$ ) / lymphocyte count ( $10^9/L$ ), while LMR as lymphocyte count ( $10^9/L$ ) / monocyte count ( $10^9/L$ ). And the SII was defined as platelet ( $10^9/L$ ) × neutrophil/ lymphocyte counts. All patients were received porta hepatis lymphadenectomy during the surgery to determine status of lymph node. Vascular invasion was defined as major vascular invasion.

Patients were followed up every 3 month after surgery. Blood tests including liver function and tumor biomarkers, and imaging examination were also performed during follow-up. Our primary end points were recurrence-free survival (RFS) and overall survival (OS). RFS was calculated from the first day after hepatectomy to the recurrence of ICC or ICC-related death, while OS was calculated from the first day after hepatectomy to the ICC-related death.

### Statistical analysis

SPSS 23.0 (SPSS Company, Chicago, IL) for Windows and Prism software (GraphPad Prism Software, La Jolla, CA) were used to analyze data and realize visualization. Independent-sample t test or Mann-Whitney U test was used to analyze the quantitative data expressed as mean±standard deviation (SD). And Chi-square or Fisher exact test was used as appropriate to analyze the categorical data expressed as frequency (percentage). The cutoff values were calculated by receiver operating characteristic (ROC)

curves. Kaplan-Meier curves were used to illustrate RFS and OS, while the log-rank test was used to detect the differences between groups. Meanwhile, the cox's proportional hazard regression was used to identify associated factors of RFS and OS.  $P < 0.05$  was considered as statistically significant.

## Results

### Patient and tumor characteristics

128 ICC patients, including 70 males and 58 females, were finally included. The basic patient and tumor characteristics were shown in Table 1. 28.1% of patients presented multiple tumors and 34.4% patients suffered from lymph node metastasis. Proportions of patients with AJCC tumor stage I, II and III were 26.6%, 14.8% and 58.6%, respectively. 39.8% patients presented vascular invasion, while 13.3% of patients had undermined liver function. The averages of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin were  $49.58 \pm 57.93$  U/L,  $42.51 \pm 31.27$  U/L and  $40.33 \pm 4.45$  g/L. The mean values of CEA, CA19-9 and CA242 were  $6.96 \pm 15.93$  ng/ml,  $272.69 \pm 318.33$  U/ml and  $75.56 \pm 104.66$  U/ml, respectively. The mean values of neutrophil, lymphocyte, monocyte and platelet counts were  $(4.70 \pm 1.91)10^9/L$ ,  $(1.59 \pm 0.49)10^9/L$ ,  $(0.66 \pm 0.87)10^9/L$  and  $(232.39 \pm 97.68)10^9/L$ , respectively. Furthermore, the mean values of calculated NLR, PLR, LMR and SII were  $3.30 \pm 2.16$ ,  $156.79 \pm 77.66$ ,  $3.20 \pm 2.46$  and  $793.67 \pm 695.14$ , respectively.

### Cutoff values of inflammatory biomarkers

ROC curves were performed to determine appropriate cutoff values of NLR, PLR, LMR and SII, and the results were shown in Figure 1. However, according to the ROC curves of RFS and OS, the results showed no significance in NLR, PLR or LMR, while significant results were shown on SII in both RFS ( $P=0.035$ ) and OS ( $P=0.034$ ) with areas under ROC curve as 0.63 (95%CI: 0.52-0.74) and 0.62 (95%CI: 0.51-0.72), respectively. Thus, the subsequent analyses were focused on SII with an ideal cutoff value as 1027 according to ROC curves and Youden index.

### Survival analyses based on SII

Survival analyses were performed between SII-low group and SII-high group according to cutoff value of SII, and the results were shown in Figure 2. The median RFS times in SII-low group and SII-high group were 16.4 months and 5.7 months, and the median OS times were 25.2 months and 10.9 months, respectively. Statistically significant differences between two groups were revealed by Kaplan-Meier curves on both RFS ( $P \leq 0.001$ ) and OS ( $P \leq 0.001$ ), indicating potential prognostic value of SII. Only one patient suffered from recurrence after 5 years (60.4 months). Another surgery was performed since the recurrence was intrahepatic and no new recurrence was found in the last follow-up.

### Univariate and multivariate analyses

For further investigating risk factors affecting RFS and OS of ICC patients, the univariate and multivariate analyses were subsequently performed among available factors, with the results shown in Table 2. The analyses revealed that multiple tumors, higher AJCC tumor stage, poorer tumor differentiation, higher level of CEA and CA19-9, higher level of SII were independently associated with both poorer RFS time and OS time. However, no significant result was shown on NLR, PLR or LMR.

## Discussion

It is widely recognized that the systemic inflammation involves in pathogenesis and progression of cancer by various mechanisms including cell proliferation, tissue infiltration and angiogenesis.<sup>11,12</sup> Multiple inflammatory biomarkers could effectively present the extent of inflammatory and immune response with high availability, therefore, were recommend as factors for predicting the prognosis of cancer patients. In the present study, we investigated the prognostic significance of inflammatory biomarkers in curative resected ICC patients. Our results suggested that SII could effectively predict the prognosis of peripheral ICC patients after curative hepatectomy, while NLR, PLR and LMR were not related with outcomes of these patients. This finding could help classifying ICC patients with a highly feasible indicator. Additional treatments, such as radiotherapy and chemotherapy, should be considered to improve the prognosis among patients with poorer prognosis predicted by SII. Furthermore, SII could serve as an indicator for planning therapies, especially immunotherapy, among ICC patients in the future.

Extensive non-specific inflammatory responses were usually led by allogeneic phenotype of cancer cell, followed by increasing of neutrophils and platelets, and decreasing of lymphocytes.<sup>13</sup> Neutrophils could secrete TNF-alpha, VEGF and interleukin, thus to promote tumor cell proliferation and angiogenesis.<sup>14</sup> Meanwhile, TGF-beta, VEGF and platelet derived factors could be secreted by platelets, accelerating differentiation and proliferation of cancer cells, and playing a significant role in adhesion and angiogenesis of tumor tissues. On the other hand, lymphocytes could mediate cytotoxicity and release cytokines, thus presenting antitumor effects as inhibiting growth, proliferation and metastasis of tumor cell.<sup>15</sup> The decrease of lymphocytes could lead to lower immune function, progression of tumor, and eventually poor prognosis of patients with tumor. Furthermore, studies showed that activity of lymphocytes could be suppressed by neutrophils.<sup>16</sup> In addition, monocytes in tumor tissues can differentiate into tumor-associated macrophages, which place promoting effects on tumor growth, tumor cell infiltration and angiogenesis.<sup>17</sup> Thus, the NLR, PLR, LMR and SII would theoretically be valuable biomarkers for predicting prognosis of cancer, considering all of them could be easily obtained from routine preoperative examinations.

In ICC, this study showed SII as the only independent risk factor on RFS and OS of patients. Two previous studies have also investigated the role of SII in OS among ICC patients.<sup>18,19</sup> Their results both indicated higher SII was associated with poorer patient survival in ICC, which was consistent with our results. However, one of them also showed that NLR had a better significance as a biomarker on ICC patient. The

inconsistent results on NLR might be caused by different cohorts because they did not focus on the patients underwent a curative therapy but the whole ICC cohort.

The present study did contain a few limitations. Firstly, this was a retrospective study with not large sample size. Further prospective, multicenter clinical studies with large cohorts should be performed to validated the values of these inflammatory biomarkers in ICC. Secondly, these inflammatory biomarkers were assessed by single measurements during admission, which might cause uncontrolled bias. Thirdly, some factors which could make an impact on these inflammatory biomarkers, such as smoking and alcoholic, were not fully under control.

## **Conclusion**

In summary, our study shows SII can effectively predict the prognosis of peripheral ICC patient undergone curative hepatectomy, while NLR, PLR and LMR are not related with clinical outcomes of these patients.

## **Abbreviations**

ICC, Intrahepatic cholangiocarcinoma

NLR, Neutrophil-to-lymphocyte ratio

PLR, Platelet-to-lymphocyte ratio

LMR, Lymphocyte-to-monocyte ratio

SII, Systemic immune-inflammation index

RFS, Recurrence-free survival

OS, Overall survival

SD, Standard deviation

ROC, Receiver operating characteristic

HBV, Hepatitis B virus

ALT, Alanine aminotransferase

AST, Aspartate aminotransferase

CEA, Carcinoembryonic antigen

## **Declarations**

## **Ethics approval and consent to participate**

The study was approved by the ethics committee of Xiangya Hospital of Central South University. Patient consent was not required to review their medical records by the ethics committee of Xiangya Hospital of Central South University because of its retrospective design, and exemption from informed consent did not adversely affect the health and rights of subjects. This study kept confidentiality of patient data and strictly complied with the Declaration of Helsinki and its later amendments or comparable ethical standards.

## **Consent for publication**

Not applicable.

## **Availability of data and material**

All data generated or analyzed during this study are included in this published article.

## **Competing interests**

The authors declare that they have no competing interests.

## **Funding**

Not applicable.

## **Authors' contributions**

All authors made substantive intellectual contributions to this study to qualify as authors. YH conceived of the design of the study. ZYZ modified the design of the study. ZYZ, YFZ, KH performed the study, collected the data, and contributed to the design of the study. ZYZ and YFZ analyzed the data. ZYZ drafted Result, Discussion, Conclusion sections. YFZ and drafted Methods sections. ZYZ, KH, YH edited the manuscript. All authors read and approved the final manuscript. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## Tables

**Table 1.** Clinicopathologic variables of included ICC patients

Variables	Values (n=128)
Age (years)	56.19±9.63
Male	70 (54.7)
Tumor size (cm)	5.83±2.85
Number of tumors	
Single	92 (71.9)
Multiple	36 (28.1)
AJCC tumor stage	
I	34 (26.6)
II	19 (14.8)
III	75 (58.6)
Lymph node metastasis	
No	84 (65.6)
Yes	44 (34.4)
Vascular invasion	
No	77 (60.2)
Yes	51 (39.8)
Tumor differentiation	
Well to moderate	44 (34.4)
Poor to undifferentiated	84 (65.6)
ALT (U/L)	49.58±57.93
AST (U/L)	42.51±31.27
CEA (ng/ml)	6.96±15.93
CA19-9 (U/ml)	272.69±318.33
CA242 (U/ml)	75.56±104.66
Neutrophil (10 <sup>9</sup> /L)	4.70±1.91
Lymphocyte (10 <sup>9</sup> /L)	1.59±0.49
Monocyte (10 <sup>9</sup> /L)	0.66±0.87
PLT (10 <sup>9</sup> /L)	232.39±97.68
Albumin (g/L)	40.33±4.45
Child-Pugh score	
A	111 (86.7)
B	17 (13.3)
NLR	3.30±2.16
PLR	156.79±77.66
LMR	3.20±2.46
SII	793.67±695.14

Data are expressed as mean±standard deviation or n (%). ICC, intrahepatic cholangiocarcinoma; AJCC, American Joint Committee on Cancer; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CEA, Carcinoembryonic antigen; PLT, Blood platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index.

**Table 2.** Univariate and multivariate analyses of risk factors with RFS and OS in ICC patients.

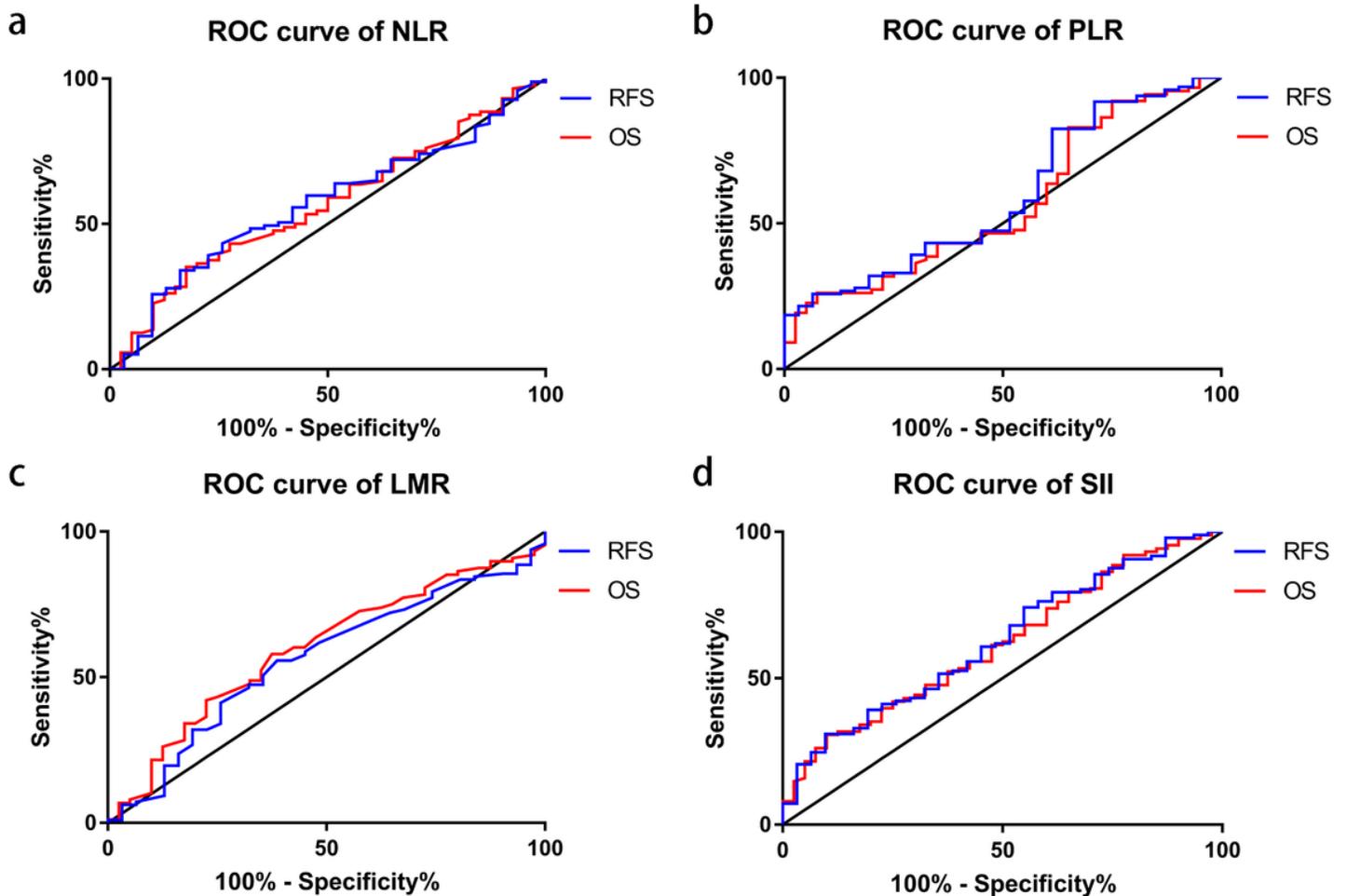
Variables	RFS		OS	
	HR (95%CI)	P value	HR (95%CI)	P value
Univariate analyses				
Age (years) ( $\geq 60$ vs. $\leq 60$ )	0.670 (0.440, 1.018)	0.061	0.794 (0.514, 1.226)	0.298
Gender (male vs. female)	0.899 (0.603, 1.341)	0.603	0.763 (0.502, 1.161)	0.207
Tumor size (cm)	1.126 (1.053, 1.204)	0.001	1.107 (1.035, 1.186)	0.003
Number of tumors (multiple vs. single)	1.797 (1.168, 2.763)	0.008	1.936 (1.246, 3.008)	0.003
AJCC tumor stage (III vs. I and II)	1.726 (1.135, 2.624)	0.011	1.960 (1.250, 3.074)	0.003
Lymph node metastasis (Yes vs. No)	1.881 (1.243, 2.848)	0.003	2.197 (1.430, 3.376)	$\leq 0.001$
Vascular invasion (Yes vs. No)	1.558 (1.041, 2.332)	0.031	1.478 (0.972, 2.248)	0.068
Tumor differentiation (poor to undifferentiated vs. well to moderate)	2.173 (1.389, 3.401)	0.001	1.971 (1.222, 3.179)	0.005
ALT (U/L)	0.998 (0.994, 1.001)	0.195	0.999 (0.995, 1.003)	0.570
AST (U/L)	0.996 (0.990, 1.003)	0.273	0.999 (0.993, 1.005)	0.815
CEA (ng/ml)	1.020 (1.008, 1.032)	0.001	1.027 (1.015, 1.040)	$\leq 0.001$
CA19-9 (U/ml)	1.002 (1.001, 1.002)	$\leq 0.001$	1.002 (1.001, 1.003)	$\leq 0.001$

CA242 (U/ml)	1.005 (1.003, 1.007)	0.001	1.005 (1.003, 1.007)	0.001
NLR	1.018 (0.947, 1.096)	0.625	1.033 (0.960, 1.112)	0.387
PLR	1.003 (1.000, 1.005)	0.021	1.003 (1.001, 1.006)	0.011
LMR	1.039 (0.943, 1.146)	0.435	1.019 (0.903, 1.151)	0.757
SII (SII-low group vs. SII-high group)	2.352 (1.519, 3.641)	0.001	2.340 (1.484, 3.689)	0.001
Albumin (g/L)	0.979 (0.936, 1.023)	0.347	0.969 (0.924, 1.017)	0.203
Child-Pugh score (B vs. A)	0.996 (0.564, 1.757)	0.988	1.286 (0.725, 2.279)	0.389
Multivariate analyses				
Tumor size (cm)	1.030 (0.953, 1.113)	0.456	0.976 (0.899, 1.060)	0.563
Number of tumors (multiple vs. single)	1.849 (1.168, 2.928)	0.009	2.017 (1.274, 3.192)	0.003
AJCC tumor stage (III vs. I and II)	1.599 (1.018, 2.511)	0.042	1.982 (1.207, 3.255)	0.007
Tumor differentiation (poor to undifferentiated vs. well to moderate)	2.355 (1.444, 3.840)	0.001	1.865 (1.093, 3.182)	0.022
CEA (ng/ml)	1.022 (1.008, 1.037)	0.003	1.033 (1.017, 1.049)	0.001
CA19-9 (U/ml)	1.001 (1.000, 1.002)	0.034	1.002 (1.001, 1.003)	0.001

CA242 (U/ml)	1.001 (0.998, 1.004)	0.552	0.999 (0.996, 1.003)	0.712
PLR	0.998 (0.995, 1.002)	0.327	0.998 (0.995, 1.002)	0.316
SII (SII-high group vs. SII-low group)	2.368 (1.279, 4.386)	0.006	2.454 (1.278, 4.712)	0.007

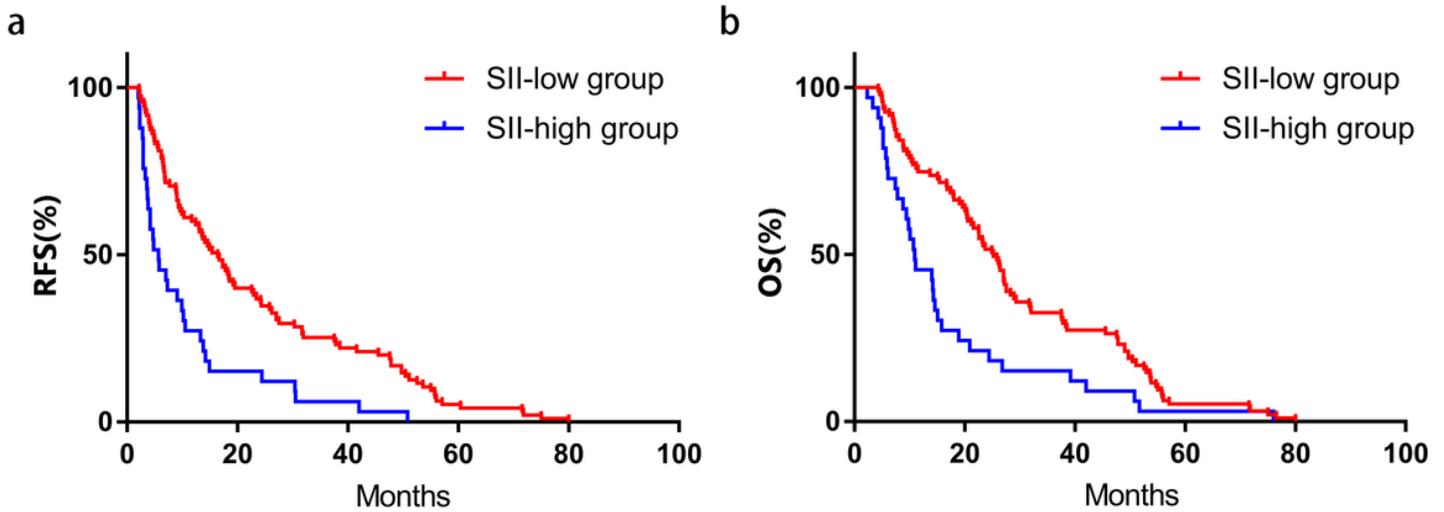
HR, hazard ratio; CI, confidence interval; ICC, intrahepatic cholangiocarcinoma; RFS, recurrence-free survival; OS, overall survival; AJCC, [American Joint Committee on Cancer](#); ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CEA, Carcinoembryonic antigen; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index.

## Figures



**Figure 1**

ROC curves of NLR(a), PLR (b), LMR (c) and SII (d) on RFS and OS. a The AUC for RFS and OS were 0.569 (95%CI=0.459-0.679, P=0.250), and 0.565 (95%CI=0.461-0.669, P=0.239). b The AUC for RFS and OS were 0.592 (95%CI=0.477-0.707, P=0.125), and 0.568 (95%CI=0.460-0.675, P=0.222). c The AUC for RFS and OS were 0.561 (95%CI=0.447-0.674, P=0.310), and 0.597 (95%CI=0.493-0.701, P=0.079). d The AUC for RFS and OS were 0.626 (95%CI=0.517-0.736, P=0.035), and 0.617 (95%CI=0.515-0.719, P=0.034). ROC, receiver operating characteristic; AUC, area under curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; RFS, recurrence free survival; OS, overall survival.



**Figure 2**

Comparisons between SII-low group and SII-high group using Kaplan-Miere curves on RFS (a) and OS (b). Better survival data were showed in SII-low group on both RFS (P<0.001) and OS (P<0.001). SII, systemic immune-inflammation index; RFS, recurrence free survival; OS, overall survival.