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ORIGINAL ARTICLE

Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected non-small cell lung cancer

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Keywords
Neutrophil-lymphocyte ratio; non-small cell lung cancer; platelet-lymphocyte ratio; prognosis; systemic immune-inflammation index.

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Abstract

Background: The systemic immune-inflammation index (SII) is correlated with patient survival in various types of solid tumors. However, only a few studies have focused on the prognostic value of the SII in patients with surgically resected non-small cell lung cancer (NSCLC).

Methods: This study was a single center retrospective analysis of 569 NSCLC patients who underwent curative lobectomy at the Department of Thoracic Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between 2006 and 2012. A receiver operating characteristic curve was plotted to compare the discriminatory ability of the SII for overall survival (OS). A Cox proportional hazards regression model was used to perform univariate and multivariate analyses.

Results: The SII, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) all correlated with OS in NSCLC patients, and the SII was an independent prognostic factor for OS (hazard ratio 1.256, 95% confidence interval 1.018–1.551; $P = 0.034$). The area under the receiver operating characteristic curve of the SII (0.547) was larger than the NLR (0.541) and PLR (0.531). Furthermore, the SII retained prognostic significance in the lung adenocarcinoma subgroup.

Conclusion: The SII is a promising prognostic predictor for patients with surgically resected NSCLC and retained prognostic significance in the lung adenocarcinoma subgroup. The prognostic value of the SII is superior to the NLR and PLR.

Introduction

Lung cancer is the most common and serious type of cancer worldwide.[1,2] There are two main types of primary lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[3,4] NSCLC accounts for approximately 85% of all new lung cancer diagnoses.[3] Currently, the clinical treatment decisions and prognostic prediction for NSCLC are based on tumor node metastasis (TNM) staging. However, because of the late and rapid clinical manifestations of occult symptoms of the disease, prognosis is extremely poor.[5] In addition, accurate TNM staging is obtained postoperatively, and preoperative prediction remains difficult. Although molecular profiling has shown great potential to guide patient management strategies, the tools are complex and expensive at present. Therefore, more potential and propagable biomarkers should be included in clinical practice to improve prognostic prediction of NSCLC.

Recently some inflammation-based parameters, such as the neutrophil-lymphocyte ratio (NLR) and platelet-

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lymphocyte ratio (PLR), have been reported to be associated with patient survival for several types of solid tumors, such as lung,[6,7] breast,[8] melanoma,[9] colorectal,[10] gastric,[11] and esophageal.[12] However, these two inflammatory indicators only integrate two types of inflammatory cells. The systemic immune-inflammation index (SII), a parameter that integrates three types of inflammatory cells (lymphocytes, neutrophils, and platelets), has been shown to be more promising than the NLR or PLR.[13–16] Three studies have reported the prognostic significance of the SII in NSCLC.[17–19] Although these studies showed that the SII was an independent prognostic predictor for NSCLC patients, their cohorts included a relatively small number of patients. Thus, we conducted the present study to investigate and verify the prognostic value of the SII in a larger cohort of patients with surgically resected NSCLC.

Methods

Patients

Medical records of 569 NSCLC patients who underwent curative lobectomy with R0 resection between July 2006 and May 2012 at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College were retrospectively reviewed. The inclusion criteria were: histologically confirmed NSCLC with complete clinical information, laboratory data, and follow-up. The exclusion criteria were: administration of neoadjuvant chemoradiotherapy; in-hospital death; and clinical evidence of chronic inflammatory, hematological, or autoimmune diseases. Patients were followed up regularly in the outpatient clinic every three to six months for the first two two years after surgery and then annually thereafter. Follow-up concluded on 27 September 2018.

The study followed the guidelines of the Helsinki Declaration and was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Informed consent was exempted for this retrospective study.

Clinicopathological parameters

Patient clinicopathological parameters, including age, gender, smoking history, pathological diagnosis, tumor differentiation grade, tumor size, lymph node metastasis, TNM stage, operation duration, intraoperative blood loss, and routine blood results, were obtained from medical records. Tumor staging was assessed according to the eighth edition of the American Joint Committee on Cancer TNM staging system.[20]

Blood sample analysis and systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) evaluations

Complete blood count data were analyzed in the general laboratory of our hospital within one week before surgery. We calculated the SII, NLR, and PLR as follows: SII = platelet count × neutrophil count/lymphocyte count, NLR = neutrophil count/lymphocyte count, and PLR = platelet count/lymphocyte count.

Statistical analysis

SPSS version 19.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. The Pearson chi-square test was used to compare categorical variables. Multiple linear regression analyses were used to determine the factors associated with the SII, NLR, and PLR. We constructed receiver operating characteristic (ROC) curves to determine the optional cutoff values for the SII, NLR, and PLR that yielded the maximum joint sensitivity and specificity. The Kaplan–Meier method was used to perform survival analyses, and the differences between the survival curves were compared by the log-rank test. We used the Cox proportional hazard model for univariate and multivariate analyses, and hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the prognostic value of the predictors. A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The 569 patients included in this study consisted of 425 (74.7%) men and 144 (25.3%) women (Table 1). The median age was 60 (range: 27–80) years. The distribution of pathological stages was as follows: stage I, 147 patients (25.8%); stage II, 177 patients (31.1%); and stage III, 245 patients (43.1%). The mean follow-up duration was 60.3 (range: 0.9–146.7) months. At the final follow-up, 345 (60.6%) patients had died.

At baseline, the median preoperative SII, NLR, and PLR values were 594.7 (range: 66.0–3394.4), 2.47 (range: 0.36–16.65), and 127.5 (range: 32.0–1088.2), respectively.

Selection of optimal cutoff values for the SII, NLR, and PLR

Previous studies have suggested different cutoff values when analyzing the prognostic value of the SII, NLR, and

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Table 1 Characteristics of the NSCLC patients grouped by SII values

Characteristic	Patients (*n*, %)	SII		*P*
		Low	High	
Gender				**0.016***
Male	425 (74.7)	183	242	
Female	144 (25.3)	79	65	
Age (years)				0.401
≤ 60	286(50.3)	137	149	
> 60	283 (49.7)	125	158	
Smoking				0.377
Ever	372 (65.4)	166	206	
Never	197 (34.6)	96	101	
Histological type				**0.014***
LUAD	295 (51.8)	153	142	
LUSC	225 (39.5)	88	137	
Others	49 (8.6)	21	28	
Tumor size				**0.001***
≤ 4	277 (48.7)	165	112	
> 4	292 (51.3)	97	195	
Differentiation				0.800
Well	182 (32.0)	83	99	
Moderately	195 (34.3)	87	108	
Poorly	192 (33.7)	92	100	
T stage				**0.000***
T1	144 (25.3)	89	55	
T2	284 (49.9)	132	152	
T3	107 (18.8)	33	74	
T4	34 (6.0)	8	26	
N stage				0.356
N0	223 (39.2)	112	111	
N1	142 (25.0)	61	81	
N2	201 (35.3)	87	114	
N3	3 (0.5)	2	1	
Lymph node metastasis				0.121
Negative	223 (39.2)	54	20	
Positive	346 (60.8)	86	40	
TNM stage				**0.001***
I	147 (25.8)	87	60	
II	177 (31.1)	77	100	
III	245 (43.1)	98	147	
Operation duration (minutes)				0.933
< 150	302(53.1)	140	162	
≥ 150	267 (46.9)	122	145	
Intraoperative blood loss (mL)				
< 150	170 (29.9)	73	97	0.359
≥ 150	399 (70.1)	189	210	
NLR				**0.001***
Low	200 (35.1)	179	21	
High	369 (64.9)	83	286	
PLR				**0.001***
Low	144 (25.3)	132	12	
High	425 (74.7)	130	295	

*$P < 0.05$ is considered significant. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NLR, neutrophil-lymphocyte ratio; NSCLC, non-small cell lung cancer; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; TNM, tumor node metastasis.

PLR. In the present study, we constructed ROC curves to determine the optional cutoff values. As shown in Figure 1, the areas under the ROC curves (AUCs) were 0.547, 0.541, and 0.531 for the SII, NLR, and PLR, respectively. The optimal cutoff values for the prediction of survival were 419.6 for the SII, 1.74 for the NLR, and 88.7 for the PLR. Consequently, we separated the patients into two groups according to the optimal cutoff values. Three hundred seven patients (54.0%) had SII values ≥ 419.6, 369 patients (64.8%) had NLRs ≥ 1.74, and 425 patients (73.8%) had PLRs ≥ 88.7.

Correlation between clinicopathological parameters and the SII, NLR, and PLR

Correlations between the clinicopathological parameters and the SII are shown in Table 1. The preoperative SII was associated with gender ($P = 0.016$), histological type ($P = 0.014$), tumor length ($P < 0.001$), T stage ($P < 0.001$), TNM stage ($P < 0.001$), NLR ($P < 0.001$), and PLR ($P < 0.001$). No other significant differences were found between the groups.

Correlations between the clinicopathological parameters and the NLR and PLR are shown in Table 2. The preoperative NLR was associated with gender ($P < 0.001$),

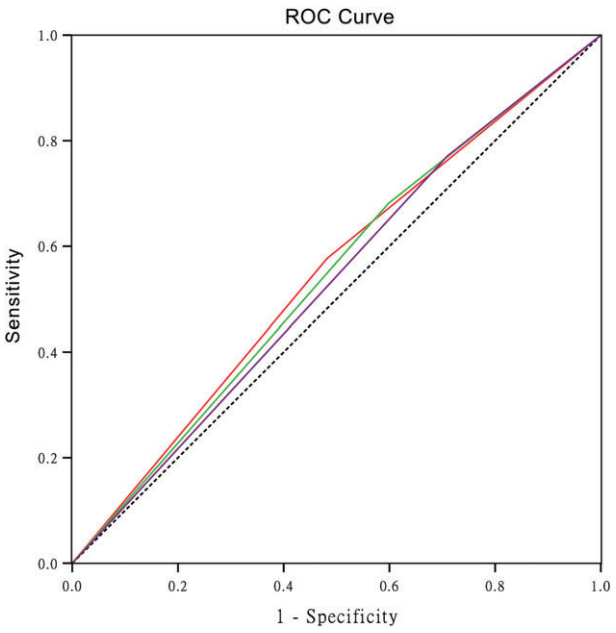

Figure 1 Receiver operating characteristic (ROC) curve analysis of the optimal cutoff value of the systemic immune-inflammation index (SII), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). The areas under the curve for overall survival were 0.547, 0.541, and 0.531 for the SII, NLR, and PLR, respectively. (——) SII, (——) NLR, (——) PLR, and (·····) Reference Line.

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Table 2 Characteristics of the NSCLC patients grouped by NLR and PLR values

Characteristic	Cases (*n*, %)	NLR		*P*	PLR		*P*
		Low	High		Low	High	
Gender				**0.001***			**0.001***
Male	425 (74.7)	121	304		122	303	
Female	144 (25.3)	79	65		22	122	
Age (years)				0.380			0.773
≤ 60	286 (50.3)	106	180		74	212	
> 60	283 (49.7)	94	189		70	213	
Smoking				**0.007***			**0.001***
Ever	372 (46.0)	116	256		111	261	
Never	197 (54.0)	84	133		33	164	
Histological type				**0.009***			0.642
LUAD	295 (51.8)	121	174		70	225	
LUSC	225 (39.5)	64	161		60	165	
Others	49 (8.6)	15	34		14	35	
Tumor length				**0.001***			**0.001***
≤ 4	277 (48.7)	124	153		89	188	
> 4	292 (51.3)	76	216		55	237	
Differentiation				0.342			0.913
Well	182 (32.0)	57	125		48	134	
Moderately	195 (34.3)	69	126		49	146	
Poorly	192 (33.7)	74	118		47	145	
T stage				**0.001***			0.072
T1	144 (25.3)	70	74		46	98	
T2	284 (49.9)	97	187		68	216	
T3	107 (18.8)	27	80		26	81	
T4	34 (6.0)	6	34		4	30	
N stage				0.235			0.249
N0	223 (39.2)	82	141		61	162	
N1	142 (25.0)	52	90		41	101	
N2	201 (35.3)	65	136		41	160	
N3	3 (0.5)	1	2		1	2	
Lymph node metastasis				0.530			0.376
Negative	223 (39.2)	36	38		61	162	
Positive	346 (60.8)	54	72		83	263	
TNM stage				0.107			0.099
I	147 (25.8)	60	87		43	104	
II	177 (31.1)	65	112		50	127	
III	245 (43.1)	75	170		51	194	
Operation duration (minutes)				0.187			0.334
< 150	302(53.1)	114	118		71	231	
≥ 150	267 (46.9)	86	181		72	194	
Intraoperative blood loss (mL)				0.848			**0.036***
< 150	170 (29.9)	61	109		33	137	
≥ 150	399 (70.1)	139	260		111	288	

*$P < 0.05$ is considered significant. LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NLR, neutrophil-lymphocyte ratio; NSCLC, non-small cell lung cancer; PLR, platelet-lymphocyte ratio; TNM, tumor node metastasis.

smoking history ($P = 0.007$), histological type ($P = 0.009$), tumor length ($P < 0.001$), and T stage ($P < 0.001$). The preoperative PLR was associated with gender ($P = 0.001$), smoking history ($P = 0.001$), tumor length ($P < 0.001$), and intraoperative blood loss ($P = 0.036$). No other significant differences were found between the groups.

Prognostic values of the SII, NLR, and PLR

We used the Kaplan–Meier method to plot the overall survival (OS) curves and compared them using the log-rank test. A high SII, NLR, and PLR were correlated with poor OS ($P = 0.001$, $P = 0.07$, and $P = 0.023$, respectively) (Fig 2a–c).

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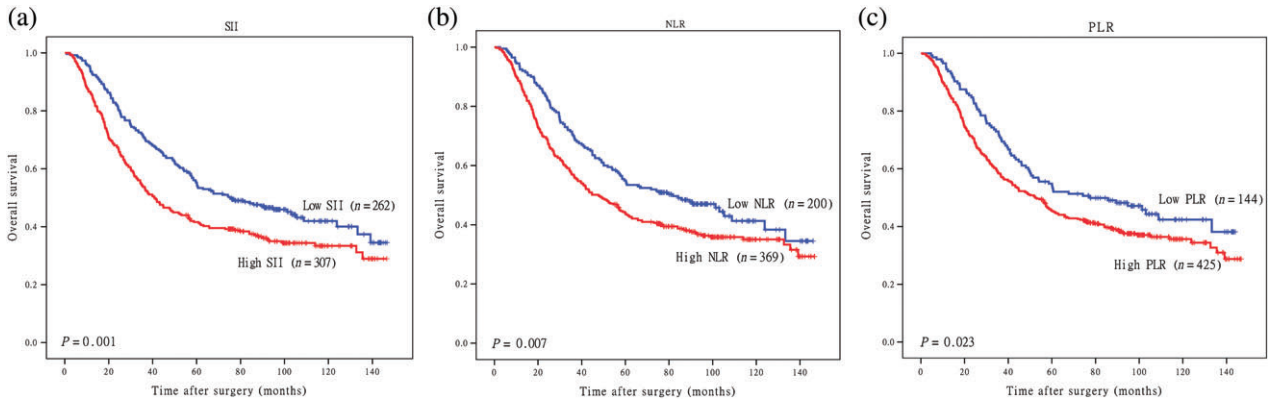

Figure 2 Kaplan–Meier overall survival curves according to the (**a**) systemic immune-inflammation index (SII), (**b**) neutrophil-lymphocyte ratio (NLR), and (**c**) platelet-lymphocyte ratio (PLR).

Moreover, we also investigated the prognostic value of the SII separately in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) subgroups. LUAD patients with higher SII values had worse OS (P = 0.001) (Fig 3a); however, the correlation in the LUSC subgroup was not statistically significant (P = 0.116) (Fig 3b).

Univariate and multivariate analyses

Univariate analyses demonstrated that age, tumor length, T stage, lymph node metastasis, TNM stage, operation duration, intraoperative blood loss, SII, NLR, and PLR were significant risk factors for poor OS (Table 3). When conducting multivariate analyses, we used three separate models to avoid multicollinearity. In each test, only one immune-inflammatory indicator (SII, NLR, or PLR) was included. The results revealed that age (P < 0.001), lymphatic metastasis (P = 0.026), TNM stage (P < 0.001), intraoperative blood loss (P = 0.039), and high SII values (P = 0.034) were independently associated with poor OS (Table 4).

Univariate and multivariate analyses were also conducted in the LUAD and LUSC subgroups. In the LUAD subgroup, univariate analyses showed that gender, age, smoking history, tumor length, tumor differentiation, T stage, lymph node metastasis, TNM stage, SII, NLR, and PLR were significant risk factors for poor OS (Table S1). The results of multivariate analyses revealed that age (P < 0.001), tumor length (P = 0.001), lymphatic metastasis (P < 0.001), high SII values (P = 0.014), and high NLR values (P = 0.003) were independently associated with poor OS (Table S2). In the LUSC subgroup, the results of univariate analyses showed that tumor differentiation, T stage, lymph node metastasis, TNM stage, and operation duration were significant risk factors for poor OS (Table S3). Multivariate analyses revealed that tumor differentiation (P = 0.032) and TNM stage (P = 0.023) were independently associated with poor OS (Table S4).

Discussion

To the best of our knowledge, compared to previous studies, our sample included the largest sample of NSCLC patients. Our study focused exclusively on the prognostic

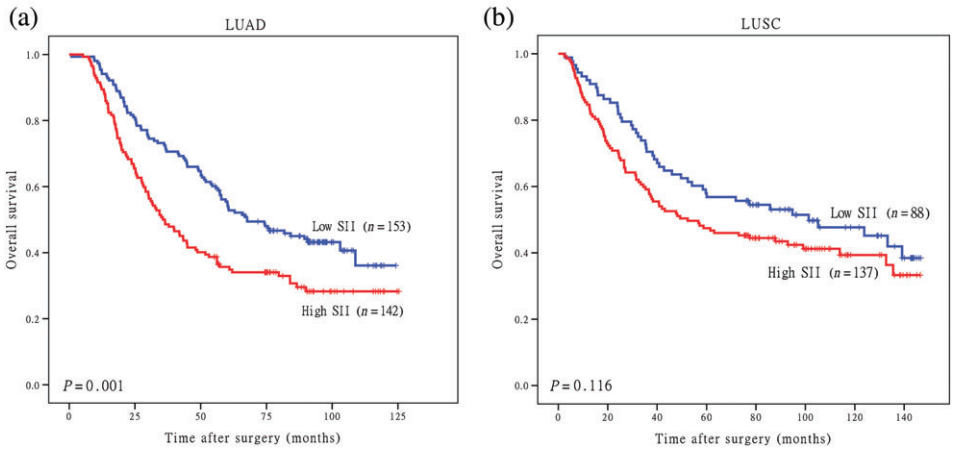

Figure 3 Kaplan–Meier overall survival (OS) curves of patients with high and low platelet-lymphocyte ratios (PLRs) stratified by histological type. OS of patients with (**a**) lung adenocarcinoma (LUAD) and (**b**) lung squamous cell carcinoma (LUSC). SII, systemic immune-inflammation index.

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Table 3 Univariate analysis of OS in NSCLC patients

Characteristic	OS		
	P	HR	95% CI
Gender (male, female)	0.242	0.862	0.673–1.105
Age (≤60, > 60 years)	**0.001***	1.564	1.263–1.937
Smoking (ever, never)	0.248	1.142	0.911–1.431
Tumor length (≤ 4, > 4)	**0.001***	1.545	1.248–1.913
Differentiation (well/moderately, poorly)	0.137	1.181	0.948–1.471
T stage (T1/T2, T3/T4)	**0.001***	1.682	1.344–2.105
Lymph node metastasis (negative, positive)	**0.001***	2.050	1.623–2.588
TNM stage (I/II, III)	**0.001***	2.270	1.834–2.810
Operation duration (minutes) (≤ 150, > 150)	**0.008***	1.333	1.079–1.647
Intraoperative blood loss (mL) (≤ 150, > 150)	**0.034***	1.299	1.020–1.655
SII (< 419.6, ≥ 419.6)	**0.001***	1.433	1.157–1.774
NLR (< 1.74, ≥ 1.74)	**0.007***	1.364	1.087–1.710
PLR (< 88.7, ≥ 88.7)	**0.024***	1.337	1.040–1.719

*$P < 0.05$ is considered significant. CI, confidence interval; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; TNM, tumor node metastasis.

Table 4 Multivariate analysis of OS in NSCLC patients

Characteristic	OS		
	P	HR	95% CI
Age (≤ 60, > 60 years)	**0.001***	1.672	1.349–2.071
Tumor length (≤ 4, > 4)	0.217	1.155	0.919–1.451
T stage (T1/T2, T3/T4)	0.326	1.139	0.878–1.479
Lymph node metastasis (negative, positive)	**0.026***	1.401	1.041–1.885
TNM stage (I/II, III)	**0.001***	1.850	1.410–2.428
Operation duration (minutes) (≤ 150, > 150)	0.340	1.109	0.897–1.372
Intraoperative blood loss (mL) (≤ 150, > 150)	**0.039***	1.291	1.085–1.667
SII (< 419.6, ≥ 419.6)	**0.034***	1.256	1.018–1.551
NLR (< 1.74, ≥ 1.74)	0.119	1.202	0.954–1.515
PLR (< 87.83, ≥ 87.83)	0.092	1.247	0.965–1.613

*$P < 0.05$ is considered significant. CI, confidence interval; HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PLR, platelet-lymphocyte ratio; SII, systemic immune-inflammation index; TNM, tumor node metastasis.

value of the SII in patients with surgically resected NSCLC. We found that the SII was associated with gender, histological type, tumor length, T stage, TNM stage, NLR, and PLR. Furthermore, the preoperative SII was an independent prognostic biomarker for OS in patients with surgically resected NSCLC, and it retained prognostic significance in the LUAD subgroup. Comparison of the AUCs showed that the prognostic ability of the SII was superior to the NLR and PLR.

Cancer-related inflammation is influential in the tumor microenvironment, and inflammatory cells in the circulation may also play important roles in tumor progression.[21] In recent years a growing body of evidence has revealed that systemic inflammation is correlated with cancer development.[22] Systemic inflammatory responses could induce tumor behavior and are associated with poor clinical outcomes in patients with various types of solid tumors.[23–26] The NLR and the PLR are two systemic inflammatory indicators; high NLR and PLR values correlate with a poor prognosis.[6,9,11,12,27] However, these two inflammatory indicators only integrate two cell types. The SII, which is based on neutrophils, platelets, and lymphocytes, seems to be a stronger prognostic predictor in a variety of solid tumors,[10,13,14] including NSCLC.[17–19]

The mechanism by which a high SII value contributes to poor survival for cancer patients remains unclear. Several theories have been proposed to explain this phenomenon. Neutrophils can activate both endothelial and parenchymal cells to enhance circulating tumor cell adhesion, promoting distant metastasis.[28] Meanwhile, circulating vascular endothelial growth factor is contained in granulocytes, particularly in neutrophils, which could be important for tumor angiogenesis.[29] Platelets can act as protective "cloaks" to shield circulating tumor cells from immune destruction, induce epithelial-mesenchymal transition, and promote distant metastasis of tumor cells.[30] Lymphocytes play an important role in immune surveillance and immune defence.[31] Meanwhile, a high density of tumor-infiltrating lymphocytes is associated with better clinical outcomes in solid tumors, and tumor-infiltrating lymphocytes are correlated with lymphocytes circulating in the peripheral blood.[32,33] Based on this information, a higher SII may be associated with tumor angiogenesis, invasion, and metastasis, thus leading to poor survival. Therefore, an elevated SII is correlated with poor survival in cancer patients.

The results of our study should be interpreted with caution. Our study was a single center retrospective study, thus selection bias was inevitable. Collaborative, multicenter, prospective studies are warranted to confirm our results.

The SII is an independent prognostic predictor in patients with surgically resected NSCLC, and the SII retained prognostic significance in the LUAD subgroup. The SII showed better prognostic ability than the NLR and PLR.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Table S1. Univariate analysis of overall survival (OS) in 295 patients with lung adenocarcinoma (LUAD).
Table S2. Multivariate analysis of overall survival (OS) in 295 patients with lung adenocarcinoma (LUAD).
Table S3. Univariate analysis of overall survival (OS) in 225 patients with lung squamous cell carcinoma (LUSC).
Table S4. Multivariate analysis with of overall survival (OS) in 225 patients with lung squamous cell carcinoma (LUSC).

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