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Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus

Ji-Feng Feng, MD*, Sheng Chen, MD, Xun Yang, MD

Abstract

The aim of the study was to determine the prognostic role of systemic immune-inflammation index (SII) in patients with esophageal squamous cell carcinoma (ESCC).

A total of 298 ESCC patients were enrolled in the current retrospective study. The SII was calculated by the formula: neutrophil × platelet/lymphocyte. The optimal cut-off value was calculated by the Cutoff Finder. Univariate and multivariate analyses were evaluated for cancer-specific survival (CSS). Additional, we also established a nomogram model to predict the prognosis for patients with ESCC.

The optimal cut-off value was 410×10^9/L for SII. Patients with SII $\leq 410(\times 10^9$/L) had a significantly better 5-year CSS than patients with SII $> 410(\times 10^9$/L) (51.9% vs 24.0%, $P < 0.001$). Multivariate analyses revealed that SII was a significant independent predictive indicator ($P = 0.027$). A nomogram could be more accuracy for CSS for patients with ESCC (c-index: 0.68).

The SII is a useful independent prognostic indicator for patients with resectable ESCC.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, EAC = esophageal adenocarcinoma, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, SII = immune-inflammation index, TNM = tumor node metastasis.

Keywords: cancer-specific survival (CSS), esophageal squamous cell carcinoma (ESCC), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognosis

1. Introduction

Esophageal cancer (EC) is one of the most fatal types of cancer wordwide, with 455,800 new cases and 400,200 deaths in 2012.[1,2] Esophageal squamous cell carcinoma (ESCC) is the predominant type in China, in contrast to the predominance of esophageal adenocarcinoma in the western countries, which covers more than 90% of all EC cases.[3,4] Surgery remains the treatment of choice for localized cancer; however, the prognosis is still poor.[5]

In recent years, inflammation plays a key role in the prognosis of cancer.[6,7] Previous studies have shown that a number of inflammatory biomarkers, such as c-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), were associated with prognosis in several types of cancer, including EC.[8–12] Recently, the systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with small cell lung cancer and hepatocellular carcinoma.[13,14] To the best of our knowledge, however, no studies regarding SII in patients with EC are available. In this study, therefore, we aimed to determine the prognostic value of SII in patients with resectable ESCC.

2. Materials and methods

A total of 298 patients with resectable ESCC were included in the current retrospective study from Jan 2005 to Dec 2008. The eligibility criteria were included: (1) ESCC diagnosed by histopathology; (2) curative surgery for localized disease (stage I–III); (3) without neoadjuvant treatment; (4) without any form of acute and/or chronic inflammatory disease; and (5) preoperative serum laboratory examination were obtained before surgery within 1 week. Patients who had received neoadjuvant therapy were excluded in the current study. The current study was approved by the Ethics Committees of Zhejiang Cancer Hospital.

Data on the preoperative laboratory examination were extracted in our medical records. The counts for neutrophil, lymphocyte, and platelet were taken within 1 week prior to surgery. The SII was defined as follows: SII = neutrophil × platelet/lymphocyte. In the current study, a cancer-specific survival (CSS) analysis was ascertained.[13,14] The last follow-up was June 2013. All patients in this study were staged according to the 7th edition Cancer Staging.[15]

2.1. Statistical analysis

Statistical analyses were conducted with SPSS 17.0 (SPSS Inc., Chicago, IL) and R 3.2.3 software (Institute for Statistics and Mathematics, Vienna, Austria). A web-based R software (Cutoff Finder) was used to determine the optimal cut-off value for SII.

Editor: Yong Liu.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:4(e5886)

Received: 25 September 2016 / Received in final form: 4 December 2016 / Accepted: 20 December 2016

http://dx.doi.org/10.1097/MD.0000000000005886

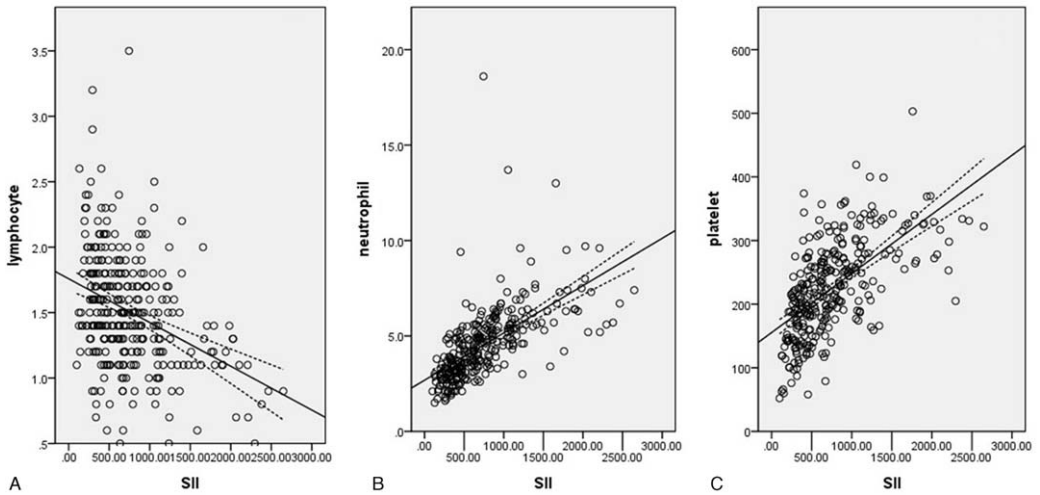

Figure 1. Pearson correlation. SII was negatively correlated with lymphocyte ($r=-0.362$, $P<0.001$; A) and positively correlated with neutrophil ($r=0.620$, $P<0.001$; B) and platelet ($r=0.607$, $P<0.001$; C). SII = immune-inflammation index.

Cutoff Finder is a freely available web application that can be accessed using an arbitrary web browser (http://molpath.charite.de/cutoff).[16] Kaplan–Meier methods were used to estimate CSS. Univariate and multivariate analyses were used to evaluate the prognostic factors. A nomogram model was also established and the predictive accuracy was evaluated by Harrell's concordance index (c-index).[17] In the current study, $P<0.05$ was considered statistically significant.

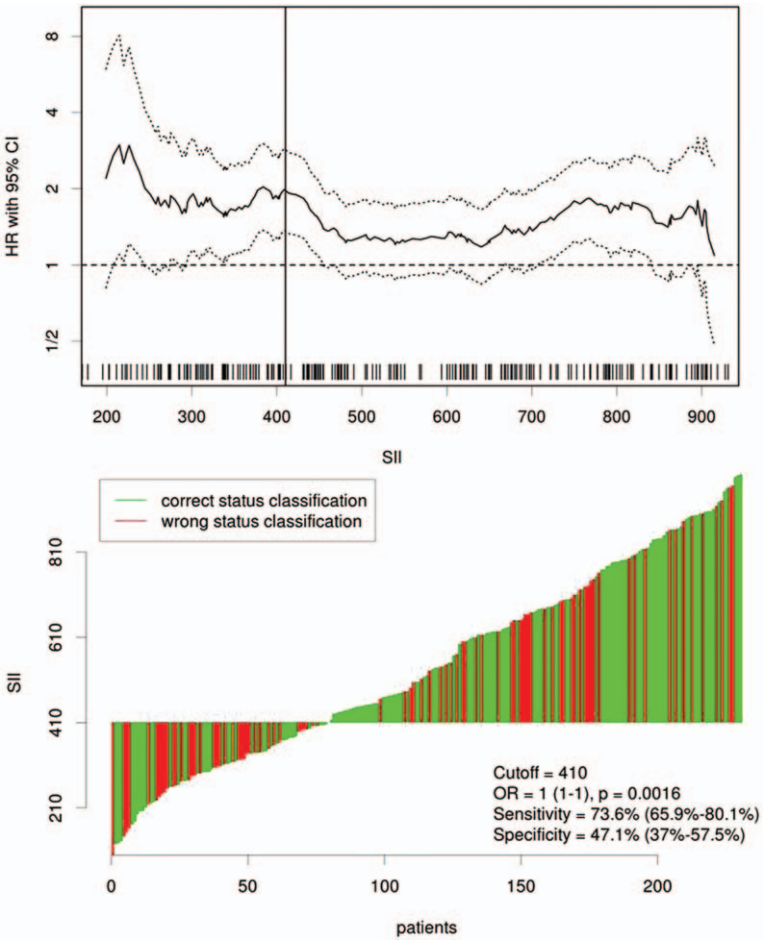

Figure 2. Cutoff Finder for optimal cut-off value of SII. The vertical line designates the optimal cut-off point with the most significant (log-rank test) split. The plots were generated using the biostatistical tool Cutoff Finder. The cut-off value was 410 with a sensitivity of 73.6% and a specificity of 47.1%. SII = immune-inflammation index.

3. Results

Of the total number of patients, 38 (12.8%) were women and 260 (87.2%) were men. The mean values for neutrophil, platelet, lymphocyte, and SII were $4.54 \pm 1.92 (\times 10^9/L)$, $225 \pm 74 (\times 10^9/L)$ and $750 \pm 482 (\times 10^9/L)$, respectively. Additionally, correlation analyses showed that SII was negatively correlated with lymphocyte ($r = -0.362$, $P < 0.001$) and positively correlated with neutrophil ($r = 0.620$, $P < 0.001$) and platelet ($r = 0.607$, $P < 0.001$) (Fig. 1).

The optimal cut-off value for SII was $410 (\times 10^9/L)$ according to the Cutoff Finder (Fig. 2). Patients then were divided into 2 groups using the SII cut-off of $410 (\times 10^9/L)$. There were 81 (27.2%) patients with SII $\leq 410 (\times 10^9/L)$ and 217 (72.8%) patients with SII $> 410 (\times 10^9/L)$. The relationships between SII and clinical characteristics were shown in Table 1. In the current study, the SII was significantly associated with tumor length ($P = 0.006$), TNM stage ($P = 0.012$), NLR ($P < 0.001$), PLR ($P < 0.001$), and CRP ($P < 0.001$).

Patients with SII $\leq 410 (\times 10^9/L)$ had a significantly better 5-year CSS than patients with SII $> 410 (\times 10^9/L)$ (51.9% vs 24.0%, $P < 0.001$) (Fig. 3A). In subgroup analyses, we revealed that SII was also significantly associated with CSS based on the TNM stage (Fig. 3B–D). The subgroup analyses based on SII for CSS were shown inTable 2. In multivariate analyses, SII was an independent prognostic factor in patients with resectable ESCC ($P = 0.027$). However, NLR ($P = 0.661$) or PLR ($P = 0.064$) were not significant independent predictors for CSS (Table 3). In the current study, we used the CRP, a well-known inflammatory indicator, in multivariate analyses. Our result revealed that CRP was still an independent prognostic factor in patients with ESCC ($P < 0.001$).

To predict the risk for patients with ESCC, a novel nomogram model was established by SII, CRP, and TNM stage combined with age and sex (Fig. 4). It can predict the probability of death for patients with ESCC. In the current study, Harrell's c-index for CSS prediction was 0.68.

Table 1

The relationship between SII and clinical characteristics in ESCC patients.

	Cases (n)	SII ($\times 10^9/L$) (mean $\pm$ SD)	*P*	SII ($\times 10^9/L$) $\leq$ 410 (%) $>$ 410 (%)	*P*
Age, y			0.365		0.195
$\leq$ 60	169	772 $\pm$ 486		41 (50.6) 128 (59.0)	
$>$ 60	129	721 $\pm$ 476		40 (49.4) 89 (41.0)	
Gender			0.134		0.514
Female	38	640 $\pm$ 369		12 (14.8) 26 (12.0)	
Male	260	766 $\pm$ 495		69 (85.2) 191 (88.0)	
Tumor length, cm			0.010		0.006
$\leq$ 5.0	207	702 $\pm$ 479		66 (81.5) 141 (65.0)	
$>$ 5.0	91	858 $\pm$ 474		15 (18.5) 76 (35.0)	
Tumor location					0.853
Upper	17	782 $\pm$ 485	Reference	5 (6.2) 12 (5.5)	
Middle	137	738 $\pm$ 478	0.718	39 (48.1) 98 (45.2)	
Lower	144	758 $\pm$ 488	0.845	37 (45.7) 107 (49.3)	
Vessel invasion			0.595		0.367
Negative	248	743 $\pm$ 476		70 (86.4) 178 (82.0)	
Positive	50	783 $\pm$ 515		11 (13.6) 39 (18.0)	
Perineural invasion			0.982		0.216
Negative	240	750 $\pm$ 495		69 (85.2) 171 (78.8)	
Positive	58	749 $\pm$ 426		12 (14.8) 46 (21.2)	
Differentiation					0.967
Well	43	780 $\pm$ 488	Reference	12 (14.8) 31 (14.3)	
Moderate	197	714 $\pm$ 457	0.394	54 (66.7) 143 (65.9)	
Poor	58	851 $\pm$ 549	0.502	15 (18.5) 43 (19.8)	
TNM stage					$<$0.001
I	74	533 $\pm$ 330	Reference	34 (42.0) 40 (18.4)	
II	99	718 $\pm$ 452	0.002	29 (35.8) 70 (32.3)	
III	131	904 $\pm$ 527	$<$0.001	18 (22.2) 107 (49.3)	
Adjuvant therapy			0.155		0.233
No	209	724 $\pm$ 460		61 (75.3) 148 (68.2)	
Yes	89	811 $\pm$ 528		20 (24.7) 69 (31.8)	
NLR			$<$0.001		$<$0.001
$\leq$ 5.0	253	612 $\pm$ 309		81 (100) 172 (79.3)	
$>$ 5.0	45	1526 $\pm$ 544		0 (0.0) 45 (20.7)	
PLR			$<$0.001		$<$0.001
$\leq$ 150	159	486 $\pm$ 244		73 (90.1) 86 (39.6)	
$>$ 150	139	1051 $\pm$ 510		8 (9.9) 131 (60.4)	
CRP, mg/L			$<$0.001		$<$0.001
$\leq$ 10.0	199	654 $\pm$ 435		69 (85.2) 130 (59.9)	
$>$ 10.0	99	942 $\pm$ 516		12 (14.8) 87 (40.1)	

CRP = c-reactive protein, ESCC = esophageal squamous cell carcinoma, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, SD = standard deviation, SII = immune-inflammation index, TNM = tumor node metastasis.

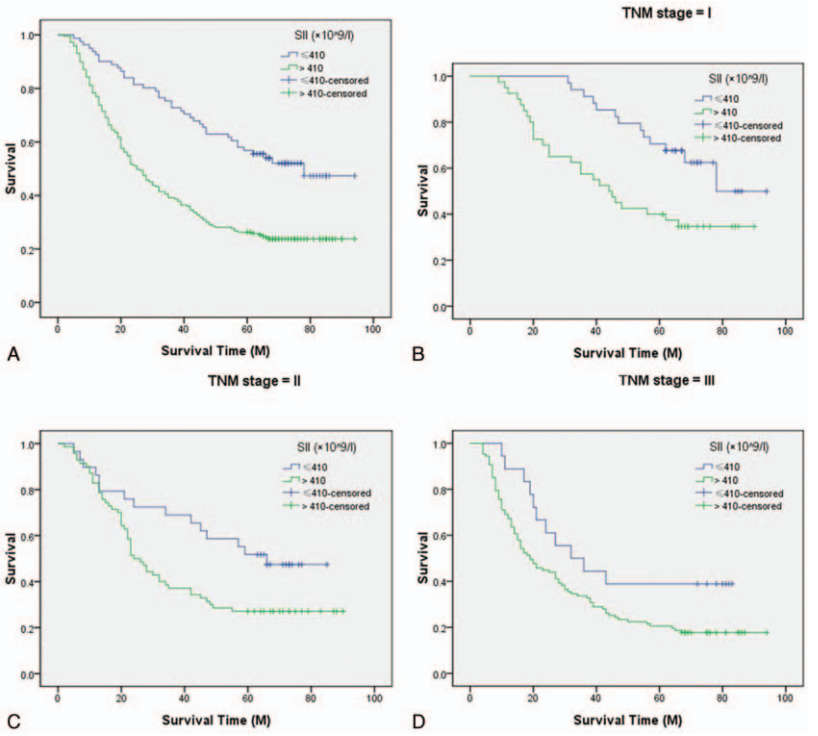

Figure 3. Kaplan–Meier CSS curves stratified by SII. Patients with SII $\leq 410 (\times 10^9/L)$ had a significantly better 5-year CSS than patients with SII $> 410 (\times 10^9/L)$ (51.9% vs 24.0%, $P < 0.001$; A). The predictive value of SII was significant in patients based on the TNM stage (I stage: 61.8% vs 35.0%, $P = 0.005$; B), (II stage: 48.3% vs 27.1%, $P = 0.028$; C), and (III stage: 38.9% vs 17.8%, $P = 0.045$; D). CSS = cancer-specific survival, SII = immune-inflammation index, TNM = tumor node metastasis.

Table 2

Subgroup analysis for CSS.

	CSS (%)	CSS (%) SII ≤ 410 ($\times 10^9$/L)	CSS (%) SII > 410 ($\times 10^9$/L)	*P*
Age, y				
≤ 60	30.8	43.9	26.6	0.007
> 60	32.6	60.0	20.2	<0.001
Gender				
Female	39.5	66.7	26.9	0.030
Male	30.4	49.3	23.6	<0.001
Tumor length, cm				
≤ 5.0	31.4	51.5	22.0	<0.001
> 5.0	31.9	53.3	27.6	0.025
Tumor location				
Upper	41.2	60.0	33.3	0.215
Middle	30.7	53.8	21.4	<0.001
Lower	31.3	48.6	25.2	0.001
Vessel invasion				
Negative	34.3	52.9	27.0	<0.001
Positive	18.0	45.5	10.3	0.017
Perineural invasion				
Negative	34.6	53.6	26.9	<0.001
Positive	19.0	41.7	13.0	0.021
Differentiation				
Well	41.9	58.3	35.5	0.149
Moderate	30.5	48.1	23.8	<0.001
Poor	27.6	60.0	16.3	0.004
TNM stage				
I	47.3	61.8	35.0	0.005
II	33.3	48.3	27.1	0.028
III	20.8	38.9	17.8	0.045
Adjuvant therapy				
No	31.6	49.2	24.3	<0.001
Yes	31.5	60.0	23.2	0.002
NLR				
≤ 5.0	34.4	51.9	26.2	<0.001
> 5.0	15.6	-	-	-
PLR				
≤ 150	41.5	53.4	31.4	<0.001
> 150	20.1	37.5	19.1	0.440
CRP, mg/L				
≤ 10.0	40.2	56.5	31.5	<0.001
> 10.0	14.1	25.0	12.6	0.098

CRP = c-reactive protein, CSS = cancer-specific survival, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, SD = standard deviation, SII = immune-inflammation index, TNM = tumor node metastasis.

4. Discussion

To the best of our knowledge, this is the first report to demonstrate the prognostic role of SII in patients with resectable ESCC. In this study, we revealed that SII was an independent significant predictive factor ($P = 0.027$). We performed a Cutoff Finder based on R software to verify to optimal cut-off value and conclude that $410 (\times 10^9/L)$ may be the optimal cut-off value for SII in predicting CSS in patients with resectable ESCC. In addition, the current study was also the first attempt to establish a predictive nomogram model to improve predictive accuracy based on SII.

There is strong linkage between cancer and inflammation. In our study, we analyzed the prognostic role of SII in ESCC patients without neoadjuvant treatment mainly because neoadjuvant therapy (chemotherapy and/or radiation) will have an important impact on the inflammation. Previous studies have shown that NLR and PLR were independent predictors of survival in various cancers, including EC.[8–12] However, due to the inconsistent results, the prognostic values of NLR and PLR in EC remain controversial.[18–20] Recently, we conducted a meta-analysis revealed that high levels of NLR were significantly correlated with poor survival in patients with EC.[21] In the current study, we revealed that preoperative NLR and PLR were all significantly associated with CSS. However, we demonstrated that PLR, but not NLR, was an independent prognostic factor in patients with resectable ESCC.

SII was initially performed to indicate the host inflammatory status in patients with resectable hepatocellular carcinoma.[13] They concluded that SII was a powerful prognostic indicator in patients with hepatocellular carcinoma. Then, another study confirmed that SII was superior to NLR and PLR as an independent factor for patients with small cell lung cancer.[14] In

Table 3

Univariate and multivariate analyses of CSS in ESCC patients.

	Univariate analysis HR (95% CI)	*P*	Multivariate analysis HR (95% CI)	*P*
Age, y		0.907	-	-
≤ 60	Reference			
> 60	1.017 (0.770–1.342)			
Gender		0.265	-	-
Female	Reference			
Male	1.280 (0.829–1.975)			
Tumor length, cm		0.373	-	-
≤ 5.0	Reference			
> 5.0	1.145 (0.849–1.544)			
Tumor location		0.725	-	-
Upper	Reference			
Middle	1.287 (0.670–2.469)	0.449		
Lower	1.303 (0.680–2.497)	0.425		
Vessel invasion		0.005		0.339
Negative	Reference		Reference	
Positive	1.643 (1.165–2.317)		1.192 (0.832–1.709)	
Perineural invasion		0.013		0.119
Negative	Reference		Reference	
Positive	1.515 (1.093–2.101)		1.306 (0.934–1.828)	
Differentiation		0.116	-	-
Well	Reference			
Moderate	1.323 (0.863–2.027)	0.199		
Poor	1.680 (1.024–2.758)	0.040		
TNM stage		<0.001		0.013
I	Reference		Reference	
II	1.670 (1.123–2.482)	0.011	1.297 (0.865–1.944)	0.208
III	2.473 (1.705–3.589)	<0.001	1.782 (1.193–2.660)	0.005
Adjuvant therapy		0.498	-	-
No	Reference			
Yes	1.109 (0.822–1.497)			
NLR		0.001		0.661
≤ 5.0	Reference		Reference	
> 5.0	1.786 (1.254–2.544)		1.088 (0.745–1.589)	
PLR		<0.001		0.064
≤ 150	Reference		Reference	
> 150	1.887 (1.430–2.489)		1.473 (0.978–2.218)	
CRP (mg/L)		<0.001		<0.001
≤ 10.0	Reference		Reference	
> 10.0	2.357 (1.778–3.124)		1.876 (1.399–2.516)	
SII ($\times 10^9$/L)		<0.001		0.027
≤ 410	Reference		Reference	
> 410	2.379 (1.675–3.378)		1.439 (1.042–1.987)	

CI = confidence interval, CRP = c-reactive protein, CSS = cancer-specific survival, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, SII = immune-inflammation index, TNM = tumor node metastasis.

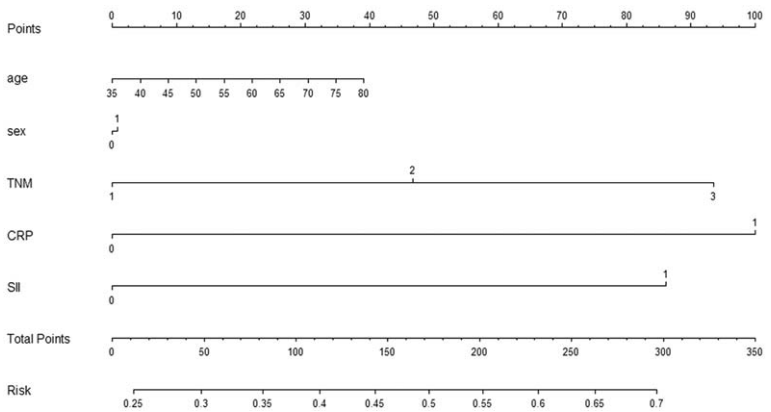

Figure 4. Nomogram model for death risk prediction. Harrell's c-index for CSS prediction was 0.68. CSS = cancer-specific survival.

the current study, we revealed that SII was a significant predictive indicator in patients with resectable ESCC ($P=0.027$). However, NLR ($P=0.661$) or PLR ($P=0.064$) were not significant independent predictors for CSS. Moreover, we used a Cutoff Finder based on R software to verify the optimal cut-off value, which was 410 ($\times 10^9$/L) compared to 330 ($\times 10^9$/L) and 1600 ($\times 10^9$/L) in previous studies.[13,14]

It is well know that nomogram could establish a simple graphic representation of a statistical predictive model.[22] In the current study, therefore, we attempt to establish a predictive nomogram model to predict the probability of the death risk for resectable ESCC patients based on SII, CRP, and TNM stage combined with age and sex. The nomogram performed well in predicting CSS by the c-index (0.68).

Several limitations should be acknowledged. First, the current study was a retrospective design with a small size population. Second, we excluded patients who had neoadjuvant chemotherapy and/or radiotherapy, which may have influenced our results. In addition, our study revealed that SII is an independent predictive factor in patients with ESCC; however, it should be kept in mind that the sensitivity and specificity looks like not very high. Moreover, the c-index showed that the nomogram model has a good accuracy but it is not perfect indicating that there is still room for improvement. Therefore, further studies are needed to illuminate the relationship between SII and prognosis in patients with resectable ESCC.

5. Conclusion

In summary, our study showed that SII is still a useful prognostic indicator for patients with resectable ESCC. We conclude that 410 ($\times 10^9$/L) may be the optimal cut-off value for SII.

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