


# Systemic immune-inflammation index predicts prognosis in patients with different EGFR-mutant lung adenocarcinoma

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## Abstract

Lung cancer is the most common type of cancer worldwide with a high mortality rate. The specific tyrosine kinase inhibitors of epidermal growth factor receptor (EGFR) have made enormous strides in non-small-cell lung cancer (NSCLC) treatment. The novel systemic immune-inflammation index (SII), a parameter that integrates lymphocytes, neutrophils, and platelets, has been found to play the vital role of a marker for predicting survival and recrudescence in various tumors.

We retrospectively examined 102 patients with different EGFR-mutant lung adenocarcinomas. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. Cut-off points were identified using the receiver operating characteristic curves with the maximum log-rank values. The Cox proportional hazards regression, expressed as p value, hazards regression, and 95% confidence interval, was conducted to assess the prognostic values of variables in overall survival (OS)/ progression-free survival (PFS).

Lower SII was associated with prolonged survival in patients with different EGFR mutant lung adenocarcinomas in both variable and multivariable analyses.

SII before treatment was a powerful indicator for the PFS and OS of patients who received the first-generation EGFR-TKI.

**Abbreviations:** ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor, HSPCs = hematopoietic stem and progenitor cells, ILs = interleukins, MLR = monocyte/lymphocyte ratio, MMPs = metalloproteinases, NLR = neutrophil/lymphocyte ratio, NSCLC = non-small-cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PLR = platelet/lymphocyte ratio, RECIST = Response Evaluation Criteria in Solid Tumors, SCLC = small-cell lung cancer, SII = systemic immune-inflammation index, TKIs = tyrosine kinase inhibitors, TNF = tumor necrosis factor.

**Keywords:** adenocarcinoma, epidermal growth factor receptor, prognosis, systemic immune-inflammation index

## 1. Introduction

Lung cancer is the most common type of cancer worldwide with a high mortality rate. The majority of patients are diagnosed at an advanced stage because the tumor is typically asymptomatic for a long time.<sup>[1,2]</sup> Primary lung cancer includes the following 2 pathological types: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts for the majority of all newly diagnosed lung cancers, which include

many pathological subtypes, such as adenocarcinoma, squamous carcinoma, and large-cell carcinoma.<sup>[3,4]</sup> Chemotherapy and radiotherapy were mainly used to treat advanced metastatic lung cancer, before the advent of targeted therapy. After treatment, the mortality rate of patients with lung cancer has not changed to a great extent.<sup>[2]</sup> Epidermal growth factor receptor (EGFR)/ERBB1/HER1, which is a member of the EGFR family, is a transmembrane protein with cytoplasmic kinase activity.

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QJ and TH contributed equally to this work.

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The specific tyrosine kinase inhibitors (TKIs) of EGFR have made enormous strides in NSCLC treatment.<sup>[5]</sup> During the last decade, EGFR-TKI has been identified as a rising star for accurate lung cancer treatment. Lung adenocarcinoma, which is the most common form of lung cancer, has a higher EGFR mutation rate (about 30%–40%) among Asian patients.<sup>[6]</sup> Many clinical trials have suggested that lung adenocarcinomas harboring the EGFR mutation treated with EGFR-TKI (erlotinib, gefitinib, or afatinib) are associated with significant improvement in progression-free survival (PFS) and objective response rate (ORR) compared with tumors treated with standard first-line chemotherapy.<sup>[7–9]</sup>

For a long time, increasing research has corroborated the role of inflammatory factors that participate in tumor shaping and metastasis.<sup>[9]</sup> Several immune-inflammation-based indexes, such as the monocyte/lymphocyte ratio (MLR), the platelet/lymphocyte ratio (PLR), and the neutrophil/lymphocyte ratio (NLR), have been proven to predict cancer recurrence and prognosis in patients with various malignant solid tumors.<sup>[10–12]</sup> The novel systemic immune-inflammation index (SII), a parameter that integrates lymphocytes, neutrophils, and platelets, has been found to be more promising than PLR, MLR, or NLR.<sup>[13–15]</sup> Previous studies have demonstrated that the SII plays the vital role of a marker for predicting survival and recrudescence in various tumors, such as esophageal cancer,<sup>[16]</sup> hepatocellular carcinoma,<sup>[15]</sup> pancreatic cancer,<sup>[17]</sup> and prostate cancer.<sup>[18]</sup>

However, there is no predictive biomarker that can be easily detected and can accurately predict the prognosis of patients with NSCLC and EGFR mutation. Therefore, our research aimed to investigate the role of the SII in predicting the prognosis of advanced lung adenocarcinoma with different EGFR mutations.

## 2. Methods

### 2.1. Ethical statement

This research was approved by the Ethics Committee of Xijing Hospital, the First Hospital affiliated to the Fourth Military Medical University.

### 2.2. Patients and follow-up

We consecutively collected the data on patients with NSCLC who harbored EGFR mutations and received EGFR-TKI treatment from January 2014 to December 2016 at Xijing Hospital. The inclusion criteria were as follows:

1. exon 19 deletion and Leu858Arg point mutation in exon 21 (L858R);
2. age range, 30 to 80 years;
3. adenocarcinoma, adenocarcinoma with squamous differentiation, or adenosquamous carcinoma;
4. EGFR-TKIs as the first-line treatment and patients who did not receive another treatment before targeted therapy;
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) from 0 to 2;
6. stages IIIb and IV.

The clinical stage evaluation at least included computed tomography scans of the chest and upper abdomen, bone, and brain. All of the patients were pathologically diagnosed according to the World Health Organization pathology classification.<sup>[19]</sup> All of the patients were routinely administered the first-generation EGFR-TKI, including gefitinib, erlotinib, or icotinib, until disease progression or intolerance to adverse

effects. Ultimately, 102 patients with advanced stage adenocarcinoma (entirely or partially) were included in our study. All of the patients were followed up through their medical records at the hospital or by telephone until March 2019. PFS referred to survival from the initiation of EGFR-TKI treatment to disease progression, which was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1), or death from other causes.<sup>[20]</sup> A total of 89 subjects showed disease progression during the follow-up, and PFS varied from 1 month to 48 months. Overall survival (OS) referred to survival from the initiation of EGFR-TKI treatment to death from any cause.

### 2.3. Statistical analyses

Survival analysis was performed using the Kaplan–Meier method with the log-rank test. Cutoff points were identified using the receiver operating characteristic curves with the maximum log-rank values. Systematic immune indexes included NLR (NLR = neutrophil count/lymphocyte count), PLR (PLR = platelet count/lymphocyte count), MLR (MLR = monocyte count/lymphocyte count), and SII (SII = platelet count × neutrophil count/lymphocyte count). The Cox proportional hazards regression, expressed as p value, hazards regression, and 95% confidence interval, was conducted to assess the prognostic values of variables in OS/PFS. The variables that were statistically significant in univariate Cox analysis were selected for the multivariate Cox analysis. All reported P values were two-sided. A *P* < .05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc, Chicago, IL).

## 3. Results

### 3.1. The SII as a prognostic factor

Ultimately, 102 patients were included in our analysis (Table 1). Among these patients, 88 subjects had pure adenocarcinoma,

**Table 1**  
Clinical characteristics of all 102 lung cancer patients.

Characteristic	Data
No. of patients	102
Age (years) Mean ± SD (range; median)	58.37 ± 10.51 (30–80; 59.50)
Gender	
Male	41 (40.2%)
Female	61 (59.8%)
Smoke status	
Never smoker	76 (74.5%)
Smoker	26 (25.5%)
Histology	
entire ADC	88 (86.3%)
partial ADC	14 (13.7%)
TNM stage	
III	23 (22.5%)
IV	79 (77.5%)
Drug	
Icotinib	21 (20.6%)
Erlotinib	15 (14.7%)
Gefitinib	66 (64.7%)
PLR Mean ± SD (range; median)	175.31 ± 90.05 (60.85–748.57; 156.11)
MLR Mean ± SD (range; median)	0.33 ± 0.23 (0.11–1.75; 0.26)
NLR Mean ± SD (range; median)	3.41 ± 1.67 (0.98–8.33; 2.95)
SII Mean ± SD (range; median)	855.31 ± 560.89 (130.21–3480.86; 712.76)
PFS (months) Median/Mean ± SD	11.00/12.79 ± 10.74
OS (months) Median/Mean ± SD	20.05/22.63 ± 13.03

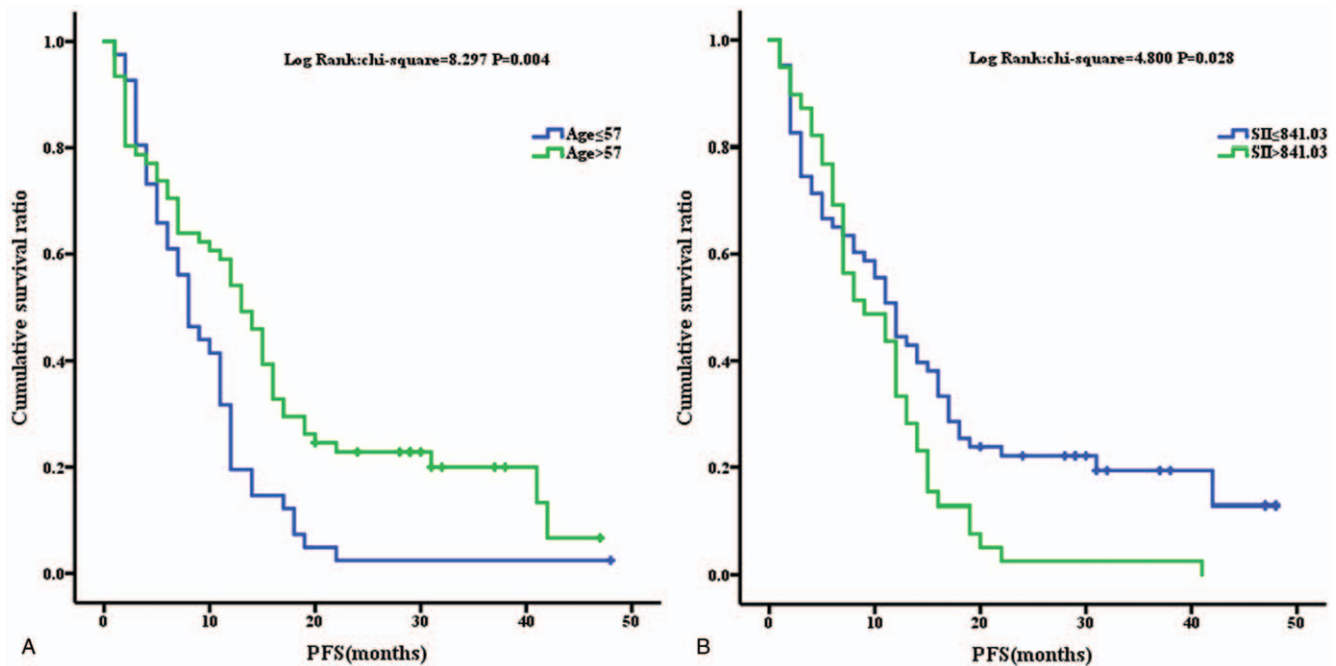


Figure 1. Kaplan–Meier analysis for PFS analysis for age (1A) and SII (1B).

whereas 14 subjects had mixed carcinoma (mainly adenosquamous carcinoma). The median age was 59.50 years, ranging from 30 years to 80 years. First-generation EGFR-TKI in our analysis included gefitinib (66 patients), erlotinib (15 patients), and icotinib (21 patients). Among these patients, females and never-smokers constituted the majority.

Using Kaplan–Meier curves, high SII values indicated a poor PFS ( $P = .028$ ) (Fig. 1) and OS ( $P = .014$ ) (Fig. 2). Otherwise, patients >57 years old had a longer PFS ( $P = .004$ ) (Fig. 1). Patients with a more advanced stage of cancer had a shorter OS ( $P = .015$ ) (Fig. 2).

### 3.2. Univariate and multivariate analyses of clinical characteristics related to long-term outcome of EGFR-TKI treatment

The cut-off values in our analyses were 57 (for age), 172.88 (for PLR), 0.23 (for MLR), 2.72 (for NLR), and 841.03 (for the SII), respectively, in this study. The Cox analysis results showed that among the inflammatory indexes, the SII was significantly associated with PFS (Univariate:  $P = .036$ , hazards ratio [HR] (confidence interval) [CI], 1.577 (1.030–2.415); Multivariate:  $P = .043$ , HR (CI), 1.555 (1.014–2.385)), whereas NLR, PLR, and MLR were not associated with PFS. Interestingly, drug selection (gefitinib, erlotinib, or icotinib) did not affect the PFS. There was no significant difference in the progression time between stages III and IV. However, elderly patients had a lower risk of early progression (Univariate:  $P = .006$ , HR (CI), 0.550 (0.358–0.843); Multivariate:  $P = .007$ , HR (CI), 0.555 (0.361–0.853)).

For the OS analysis, stage and SII were independent prognostic factors for patients who received EGFR-TKI treatment ( $P = .043$  and  $.049$ , respectively) (Table 3). Neither smoking status nor

gender had a significant influence on the OS. Similarly, any kind of first-generation EGFR-TKI was available ( $P = .322$ ). Once the EGFR mutant status was suitable, pure adenocarcinoma and partial adenocarcinoma did not exhibit a significant difference in the long-term prognosis (Tables 2 and 3).

### 3.3. Subgroup analyses

For PFS, the SII was significant in never-smokers ( $P = .031$ ) and had edge significance in the female subgroup ( $P = .050$ ), whereas SII demonstrated no statistical significance in the other subgroups with the limitation of sample size (Table 4). This meant that the SII might be more significant in females and never-smokers who received EGFR-TKIs for predicting disease progression. However, for OS, the SII was a significant predictive factor in male and stage IV patients. Interestingly, the SII was more effective in stage IV patients, which indicated that the inflammatory status was more essential for the OS of patients with more advanced stages of cancer.

## 4. Discussion

The SII, a novel biomarker, has been shown to be correlated with poor prognosis in patients with lung cancer. As already known, the SII is calculated on the basis of the peripheral lymphocyte, neutrophil, and platelet blood counts; these 3 types of cells are involved in the inflammatory response of the human body. To date, many studies have confirmed that the inflammatory reaction in the human body is closely related to the occurrence and development of tumors.<sup>[21,22]</sup>

Therefore, the SII is regarded as a valuable and trustworthy noninvasive indicator for evaluating the survival and prognosis in patients with tumors.<sup>[13,16–18]</sup> In recent years, an increasing number of clinical studies have confirmed that

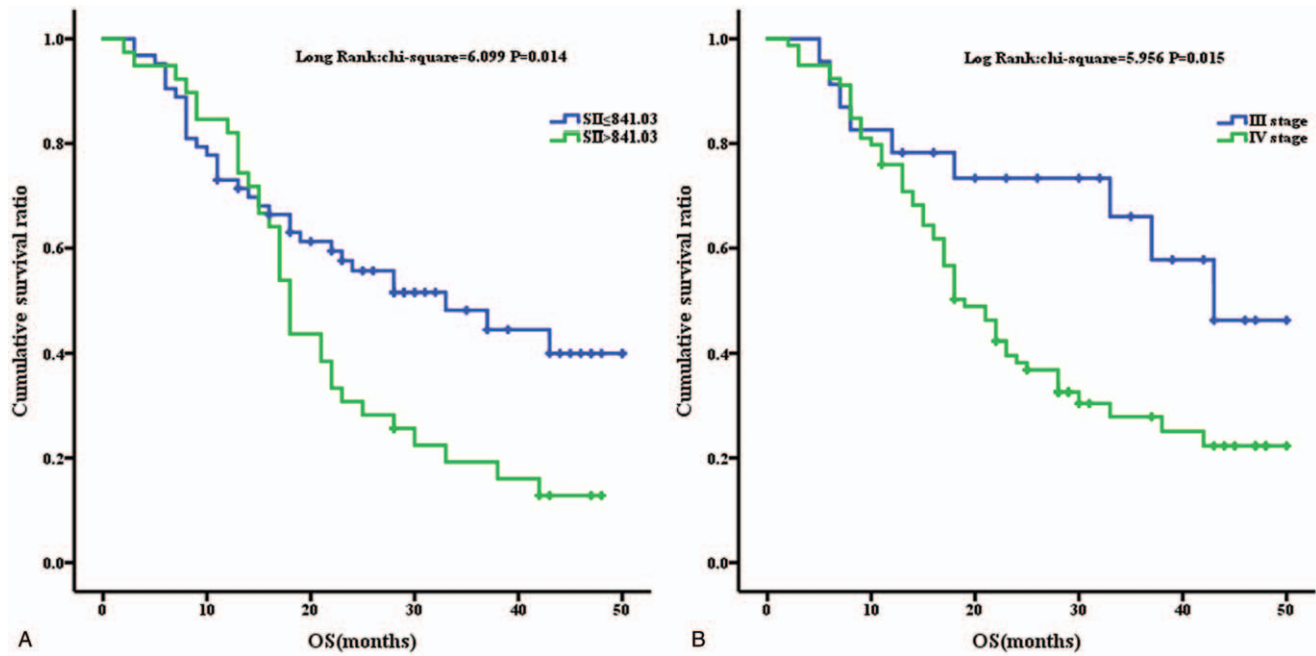


Figure 2. Kaplan–Meier analysis for OS analysis for SII (2A) and Stage (2B).

Table 2

Univariate and multivariate proportional hazards (Cox) regression analyses according to PFS.

Variables in the equation	Univariate Cox analysis		Multivariate Cox analysis	
	P	Hazard ratio (95%CI)	P	Hazard ratio (95.0% CI)
Age				
<57	–	–	–	–
>57	.006	0.550 (0.358–0.843)	.007	0.555 (0.361–0.853)
Gender				
Male	–	–		
Female	.410	0.837 (0.549–1.277)		
Smoke status				
Never	–	–		
Smoker	.313	1.273 (0.796–2.034)		
Histology				
ADC	–	–		
Others	.391	0.766 (0.416–1.409)		
TNM stage				
III	–	–		
IV	.500	1.191 (0.717–1.978)		
PLR				
<172.88	–	–		
>172.88	.137	1.385 (0.902–2.127)		
MLR				
<0.23	–	–		
>0.23	.055	1.557 (0.990–2.450)		
NLR				
<2.72	–	–		
>2.72	.092	1.453 (0.940–2.246)		
SII				
<841.03	–	–	–	–
>841.03	.036	1.577 (1.030–2.415)	0.043	1.555 (1.014–2.385)
Drug				
Icotinib	.792	–		
Erlotinib	.736	0.884 (0.431–1.812)		
Gefitinib	.464	0.832 (0.490–1.413)		

**Table 3**  
Univariate and multivariate proportional hazards (Cox) regression analyses according to OS.

Variables in the equation	Univariate Cox analysis		Multivariate Cox analysis	
	P	Hazard ratio (95% CI)	P	Hazard ratio (95.0% CI)
Age				
<57	–	–		
>57	.360	0.793 (0.483–1.303)		
Gender				
Male	–	–		
Female	.572	0.865 (0.523–1.430)		
Smoke status				
Never	–	–		
Smoker	.946	1.020 (0.572–1.818)		
Histology				
ADC	–	–		
Others	.462	0.745 (0.340–1.633)		
TNM stage				
III	–	–	–	–
IV	.020	2.326 (1.145–4.724)	0.043	2.096 (1.022–4.299)
PLR				
<172.88	–	–		
>172.88	.053	1.621 (0.993–2.646)		
MLR				
<0.23	–	–		
>0.23	.055	1.690 (0.989–2.887)		
NLR				
<2.72	–	–		
>2.72	.140	1.469 (0.881–2.448)		
SII				
<841.03	–	–	–	–
>841.03	.017	1.817 (1.114–2.961)	0.049	1.644 (1.002–2.696)
Drug				
Icotinib	.322	–		
Erlotinib	.141	0.509 (0.207–1.251)		
Gefitinib	.324	0.742 (0.411–1.341)		

the SII can predict the prognosis and the recurrence of lung cancer in patients. Li et al suggested that the decrease in SII values was associated with longer survival time in patients with brain metastasis from lung cancer, irrespective of whether there was an EGFR mutation.<sup>[2,3]</sup> Besides, Hong

et al found that the patients with small-cell lung cancer who have SII  $>1600 \times 10^9/L$  may have worse prognosis than patients with low SII values.<sup>[24]</sup> Consequently, scholars began to pay increased attention to the clinical significance of the SII in guiding the prognosis of patients with lung cancer.

**Table 4**  
subgroup analyses according to PFS and OS.

Variables in the equation	PFS		OS	
	P	Hazard ratio (95% CI)	P	Hazard ratio (95.0% CI)
Age				
<57	.300	1.401 (0.740–2.653)	.054	2.153 (0.988–4.691)
>57	.071	1.697 (0.956–3.013)	.191	1.534 (0.808–2.912)
Gender				
Male	.451	1.298 (0.659–2.557)	.015	2.709 (1.212–6.052)
Female	.050	1.754 (1.000–3.077)	.271	1.419 (0.761–2.647)
Smoke status				
Never	.031	1.730 (1.051–2.850)	.054	1.726 (0.990–3.012)
Smoker	.891	1.063 (0.444–2.548)	.014	2.185 (0.774–6.165)
Histology				
ADC	.130	1.423 (0.901–2.248)	.068	1.627 (0.965–2.743)
Others	.072	3.922 (0.885–17.376)	.134	3.570 (0.675–18.876)
TNM stage				
III	.177	2.268 (0.691–7.441)	.931	1.072 (0.221–5.199)
IV	.127	1.443 (0.901–2.311)	.041	1.740 (1.024–2.959)

Although EGFR-targeted therapy has produced prominent effects in alleviating tumor progression in patients with advanced NSCLC harboring the indicated driven-mutations,<sup>[25,26]</sup> several variations of molecular phenotypes may lead to tumor recurrence and poor prognosis in an acquired-drug resistance manner. The occurrence of a secondary mutation, especially the T790M substitution in exon 20 of the EGFR kinase domain, acts as one of the most common mechanisms in mediating acquired resistance to gefitinib, the first-generation EGFR-TKI.<sup>[27]</sup> This abnormal gene expression weakens the combination between targeted drugs and the ATP-binding sites in EGFR, leading to continuous activation of EGFR-induced downstream signaling, and in turn, gives rise to resistance features.<sup>[28]</sup> The activation of an alternative pathway reveals another resistance mechanism, which activates the cytokine receptor on the membrane in an EGFR-independent manner and initiates the same signaling pathway with EGFR. The amplification of MET, a transmembrane tyrosine kinase receptor, has been viewed as a typical mutant oncogene in bypass activation.<sup>[29]</sup> Additionally, there is phenotype transformation from NSCLC to SCLC.<sup>[30]</sup>

In vitro experiments and clinical and epidemiologic studies, increasing evidence suggests that inflammatory response, immune microenvironment, and tumorigenesis are closely related to one another.<sup>[31,32]</sup> These theories might explain the mechanism of the high SII value associated with poor survival in patients with lung cancer. As early as the 19th century, Rudolf Virchow observed the presence of leukocytes within tumors. Subsequent studies found that inflammatory responses play a decisive role in nearly all stages of tumor development.<sup>[22,33–35]</sup> Current research reveals that hematopoiesis defects and immunosuppression may play an important role in tumor progression. In a stable state, the development of blood cell lines is strictly controlled by endogenous signals, which promote continuous differentiation of hematopoietic stem and progenitor cells (HSPCs).<sup>[36]</sup> Several studies found that HSPCs express receptors for various cytokines and microbial products. They inferred that hematopoiesis functions play a critical role in the primary immune response to tumors.<sup>[37–39]</sup> Therefore, it will lead to destruction of hematopoietic homeostasis in the process of tumor development, including myelopoiesis and leukocytosis. The present study showed that peripheral blood hematopoietic precursors could selectively lose lymphoid potential and skew towards granulocyte differentiation in patients with tumors.<sup>[40]</sup> Accordingly, increased number of peripheral neutrophils and NLR could serve as indicators for poor prognosis in patients with different types of tumors.

Macrophages, lymphocytes, neutrophils, and dendritic cells belong to the leukocyte population. They take part in the invasion, metastasis, and angiogenesis of lung cancer cells by releasing a variety of cytokines, cytotoxic mediators, and chemokines, such as reactive oxygen species, metalloproteinases (MMPs), and membrane perforator agents, and soluble mediators of cell death, such as tumor necrosis factor (TNF)- $\alpha$ , interleukins (ILs), and interferons.<sup>[41]</sup> Karin et al. suggested that NF- $\kappa$ B and proinflammatory cytokines, such as IL-1 $\beta$  and TNF- $\alpha$ , are involved in promoting cancer cell proliferation by interacting with each other.<sup>[42]</sup> MMPs are a family of proteolytic enzymes that include MMP-1, -3, -7, and -9. Liu et al. reported that polymorphisms in the promoter regions of MMP-1, -3, -7, and -9 might be associated with metastasis in many cancers, such as lung cancer, breast cancer, and head/neck cancer.<sup>[43,44]</sup> Additional studies suggested that they not only participate in

lung cancer metastasis but also in nearly all stages of cancer progression.<sup>[45]</sup>

However, this study has several limitations. This is a single-center, retrospective study. The number of samples included in the study is limited. The results of our study should be interpreted with caution. A multicenter, prospective study with a large population size is needed to confirm our results. Besides, tumor-associated macrophages (TAMs), which originate from circulatory monocytes, play an important part in the tumor microenvironment. Numerous data have revealed that TAMs are closely correlated with cancer progression.<sup>[46,47]</sup> Moreover, many previous studies have shown that the peripheral monocyte count is a useful prognostic marker.<sup>[48–50]</sup> However, monocytes are not included in the index. A more accurate index, which can combine them together, is needed to better predict the prognosis of EGFR-mutant lung adenocarcinoma. Nonetheless, to the best of our knowledge, this is the first study to evaluate the impact of relatively comprehensive inflammation-based scores (SII) on the prognosis of NSCLC with EGFR mutations in patients who received the first-generation EGFR-TKI.

## 5. Conclusion

Systemic immune and inflammation status was closely related to disease progression in patients with advanced lung adenocarcinoma. The SII before treatment was a powerful indicator for the PFS and OS in patients who received the first-generation EGFR-TKI.

## Author contributions

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**Project administration:** Qing Ju, Tingping Huang, Jian Zhang.

**Writing – original draft:** Qing Ju, Tingping Huang, Yong Zhang.

**Writing – review & editing:** Lei Wu, Jing Geng, Xiaoyan Mu, Tao Yan, Jian Zhang.

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