

Systemic Inflammation Response Index (SIRI) Independently Predicts Survival in Advanced Lung Adenocarcinoma Patients Treated with First-Generation EGFR-TKIs

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Background: Systemic inflammation response index (SIRI) has been reported to be an effective blood-based biomarker for predicting prognosis in various kinds of cancer patients. However, the prognostic role of SIRI in advanced lung adenocarcinoma patient remains unclear. **Methods:** The aim of the present study is to evaluate the prognostic role of SIRI in EGFR-mutant advanced lung adenocarcinoma patients treated with first-generation EGFR-TKIs. A total of 245 patients who received gefitinib, erlotinib, or icotinib at the Second Xiangya Hospital were retrospectively evaluated. SIRI was defined as neutrophil count \times monocyte/lymphocyte count. The optimal cut-off value was determined according to receiver operation characteristic curve analysis. Characteristics of patients were compared via chi-square test or Fisher's exact test. Survivals were estimated by the Kaplan–Meier method and compared by the Log rank test. Multivariate analysis was estimated using the Cox proportional hazards model.

Results: It is showed that high SIRI was associated with male patient, smoker, worse ECOG PS, 19-DEL mutation. Kaplan–Meier survival analysis showed that ECOG PS, brain metastasis, SIRI were significantly correlated with progression-free survival (PFS), and gender, ECOG PS, brain metastasis, NLR and SIRI were significantly correlated with overall survival (OS). Multivariate analysis showed that SIRI and ECOG PS independently predict PFS and OS.

Conclusion: Our findings indicate that SIRI is an effective and convenient marker for predicting prognosis in advanced EGFR-mutant lung adenocarcinoma patients treated with first-generation TKI.

Keywords: lung adenocarcinoma, EGFR-TKI, SIRI, prognosis

Introduction

Lung cancer is the leading cause of mortality both in China and worldwide, among which non-small cell lung cancer consists of more than 80% of the patients.¹ In China, more than half of the patients are diagnosed at advanced stage, and the prognosis is poor. Based on serials of clinical trials, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been established as the optimal choice of advanced NSCLC patients harboring EGFR active mutations.^{2–4} However, nearly all the patients will inevitably suffer from drug resistance which cause treatment failure. Therefore, exploring biomarkers to predict patients' prognosis and facilitate patient stratification is urgently needed in clinical practice.

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Tumor promotion inflammation is a hall mark of cancer.⁵ Local and systemic inflammation significantly affects tumor progression and its response to therapy. There is increasing evidence showing that inflammation indexes could be used to predict the prognosis of cancer patients. The immune and inflammatory cells, including neutrophil, monocyte, lymphocyte, and platelet, which can be detected in circulation blood may contribute to cancer invasion and metastasis.⁶ And anti-inflammation intervention is a promising strategy to further improve the effectiveness of anti-tumor treatment.⁷ Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are widely studied markers which are proven to be effective in predicting patients' survival in various kinds of cancer patients.^{8–11} The systemic inflammation response index (SIRI) is defined as neutrophil count \times monocyte/lymphocyte count, which can better reflect the host immune and inflammation balance. It has been reported that SIRI could predict survival in various kinds of cancers, including pancreatic cancer,¹² gallbladder cancer,¹³ oral squamous cell carcinoma,¹⁴ and cervical cancer.¹⁵ The report on the prognostic role of SIRI in lung cancer is rare. Liu et al reported that higher preoperative SIRI could predict poorer survival in surgically resected NSCLC.¹⁶ However, the prognostic role of SIRI in advanced stage NSCLC patients remain to be elucidated.

In the present study, a cohort of 245 EGFR-mutant advanced lung adenocarcinoma patients were retrospectively analyzed to evaluate the clinical significance and prognostic value of NLR, PLR, and SIRI in NSCLC patients receiving first-generation EGFR-TKIs treatment.

Patients and Methods

Patient Selection

We retrospectively enrolled 245 lung adenocarcinoma patient who received first-generation EGFR-TKI as first-line treatment from January 2017 to June 2019 at the Second Xiangya Hospital, Central South University, Changsha, China. All the clinical data were obtained from electronic medical record system. The inclusion criteria were as follows: (1) pathologically diagnosed lung adenocarcinoma; (2) harboring EGFR active mutation; (3) suffering relapsed or metastasized disease (stage IV according to AJCC/UICC staging system); (4) using first-generation EGFR-TKI (gefitinib, erlotinib, or icotinib) as the first-line treatment; (5) with complete record of blood test results within 1 week prior to the initiation of EGFR-

TKI treatment and follow-up data. The exclusion criteria were as follows: (1) history of other malignant tumors and chronic inflammatory diseases (for example: inflammatory bowel disease); (2) steroid therapy within 2 weeks before the initiation of EGFR-TKI treatment; (3) with recent clinical evidence of acute infection or inflammation; (4) Antiangiogenic drugs (avastin) and/or chemotherapy drugs were used accompanied with EGFR-TKI during the first-line treatment. This study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. Written consent was waived due to the retrospective nature of the study, and patient data confidentiality rules are in compliance with the Declaration of Helsinki.

Data Collection and Follow-Up

Patient clinicopathological characteristics including gender, age, smoking history, brain metastasis status, ECOG score, EGFR mutation status, and full blood counts within 1 week of the initiation of EGFR-TKI treatment were obtained from the electronic medical record system of the Second Xiangya Hospital. The SIRI, NLR, and PLR were calculated as follows: SIRI = neutrophil count \times monocyte/lymphocyte count, NLR = neutrophil counts/lymphocyte counts, PLR = platelet counts/lymphocyte counts. The patient was followed up by outpatient examination or telephone interview at about every 2 months. The last follow-up date was April 30, 2020. The overall survival (OS) was defined as the interval between the date of first day of EGFR-TKI administration and the date of death for any reason or to the last date of follow-up. The progression-free survival (PFS) was defined as the interval between the date of first day of EGFR-TKI administration and the date of disease progression based on response evaluation criteria in solid tumors (RECIST) 1.1, or death.

Statistical Analysis

The relationship between SIRI, NLR, and PLR and clinicopathological factors were analyzed using the chi-square test. The optimal cut-off value for SIRI, NLR, and PLR was determined by receiver operating characteristic (ROC) curves analysis using the highest Youden index, defined as sensitivity+specificity-1, to predict PFS. Survival analysis was performed using Kaplan–Meier method. The differences between the survival curves were compared by Log rank test. The multivariate Cox hazard regression analysis was performed on the factors that were shown to be significant on univariate analysis. All tests were 2-sided and

P values less than 0.05 were considered significant. The SPSS software 23.0 (IBM Corp., Armonk, NY) was used.

Results

Patient Characteristics

In the present study, we enrolled 245 patients, and the baseline clinicopathological characteristics were shown in Table 1. There were 107 (43.7%) male patients and 138 (56.3%) female patients. The median age was 60 years (range: 28–88 years). Sixty-nine patients (28.2%) had a smoking history. The majority of patients had an ECOG score of 0 to 1 (204, 83.3%). In all the patients,

Table 1 Clinicopathological Characteristics of 245 Patients

Characteristics	Number (%)
Age	
Median	60
Range	28–88
Gender	
Male	107(43.7)
Female	138(56.3)
Smoking status	
Non-smoker	176(71.8)
Current or ex-smoker	69(28.2)
ECOG PS	
0	38(15.5)
1	166(67.8)
2	41(16.7)
Brain metastasis	
Yes	26(10.6)
No	219(89.4)
EGFR mutation	
L858R	101(41.2)
19-DEL	134(54.7)
Other	10(4.1)
NLR	
High	82(33.5)
Low	163(66.5)
PLR	
High	52(21.2)
Low	193(78.8)
SIRI	
High	90(36.7)
Low	155(63.3)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SIRI, systemic immune response index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

101 (41.2%) patients had the exon 21 L858R mutation, 134 (54.7%) the exon 19 deletion mutation, and 10 (4.1%) other rare mutations. There are 26 (10.6%) patients who had brain metastasis, and 10 patients received whole brain radiation therapy (WBRT) concurrent with TKI. The median follow-up period was 18.3 months (range 2.2–37.8 months). At the final follow-up, 119 (48.6%) patients had died and 153 (62.4%) patients suffered from disease progression.

Relationship Between SIRI, NLR, PLR, and Clinicopathological Characteristics

The optimal cut-off value for SIRI, NLR and PLR were calculated using receiver operation characteristic curve analysis for PFS, and the optimal cut-off value were 0.71, 3.36, and 167.01 respectively, with an area under the curve of 0.577, 0.516, and 0.513 (Figure S1). As shown in Table 2, high SIRI was associated with male patient, smoker, worse ECOG PS, 19-DEL mutation. High NLR was associated with male patient, worse ECOG PS, and 19-DEL mutation. High PLR was associated with worse ECOG PS.

Univariate and Multivariate Cox Regression Analysis for PFS and OS

On univariate cox regression analyses, ECOG PS, brain metastasis, and SIRI were associated with PFS ($P=0.007$, 0.043, 0.002, respectively). And ECOG PS, gender, brain metastasis, NLR and SIRI were associated with OS ($P<0.001$, 0.010, 0.038, 0.004, and 0.001, respectively) (Table 3, and Figure 1). All other clinicopathological characteristics were not statistically significant. In the multivariate Cox regression analysis, as shown in Table 4, ECOG PS (HR 2.562; 95% CI 1.667–3.940; $P<0.001$), and SIRI (HR 2.384; 95% CI 1.275–4.459; $P<0.007$) were independent prognostic factors for PFS. And ECOG PS (HR 2.431; 95% CI 1.571–3.761; $P<0.001$), and SIRI (HR 1.721; 95% CI 1.024–3.898; $P=0.042$) were also independent prognostic factors for OS.

Discussion

NSCLC is the most common malignancies worldwide. For patients with EGFR mutation, EGFR-TKIs have been established as the cornerstone of the treatment of advanced stage patients. Serial trials have demonstrated that patients treated with first-generation EGFR-TKIs have longer PFS and quality of life, compared with chemotherapy.¹⁷

Table 2 The Association of SIRI, NLR, and PLR with Clinicopathologic Characteristics in 245 Patients with Advanced Lung Adenocarcinoma

Characteristics	SIRI <0.71	SIRI ≥0.71	P	NLR <3.36	NLR ≥3.36	P	PLR <167.01	PLR ≥167.01	P
Age									
<65	41(16.7%)	136(55.5%)	0.606	102(41.6%)	75(30.6%)	0.251	87(35.5%)	90(36.7%)	0.669
≥65	13(5.3%)	55(22.4%)		33(13.5%)	35(14.3%)		36(14.7%)	32(13.1%)	
Gender									
Female	42(17.1%)	96(39.2%)	<0.001	85(34.7%)	53(21.6%)	0.028	68(27.8%)	70(28.6%)	0.797
Male	12(4.9%)	95(38.8%)		50(20.4%)	57(23.3%)		55(22.4%)	52(21.2%)	
Smoking status									
No	47(19.2%)	129(52.7%)	0.006	98(40.0%)	78(31.8%)	0.777	83(33.9%)	93(38.0%)	0.156
Yes	7(2.9%)	62(25.3%)		37(15.1%)	32(13.1%)		40(16.3%)	29(11.8%)	
ECOG PS									
0–1	50(20.4%)	154(62.9%)	0.039	121(49.4%)	83(33.9%)	0.004	111(45.3%)	93(38.0%)	0.004
2	4(1.6%)	37(15.1%)		14(5.7%)	27(11.0%)		12(4.9%)	29(11.8%)	
Brain metastasis									
No	47(19.2%)	172(70.2%)	0.616	122(49.8%)	97(39.6%)	0.678	110(44.9%)	109(44.5%)	1.000
Yes	7(2.9%)	19(7.8%)		13(5.3%)	13(5.3%)		13(5.3%)	13(5.3%)	
EGFR mutation									
19-DEL	27(11.0%)	107(43.7%)	0.001	70(28.6%)	64(26.1%)	0.014	63(25.7%)	71(29.0%)	0.125
L858R	20(8.2%)	81(33.1%)		55(22.4%)	46(18.8%)		52(21.2%)	49(20.0%)	
Other	7(2.9%)	3(1.2%)		10(4.1%)	0(0%)		8(3.3%)	2(0.8%)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SIRI, systemic immune response index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

However, the median PFS of first-line EGFR-TKIs treatment is about 8–12 months, and nearly all the patient will be suffered from drug resistance. The markers with prognostic value in predicting the survival of the patients are lacking. Therefore, it is important to find reliable tumor markers of prognosis and facilitate treatment adjusting and patient stratification. In the present study, we evaluated prognostic effect of blood-based immune-inflammation indexes, including SIRI, NLR and PLR in EGFR-mutant advanced lung adenocarcinoma treated with first-generation EGFR-TKIs. And we found that SIRI and ECOG PS are independent prognostic factors of PFS and OS in advanced lung adenocarcinoma patients.

Inflammation is a hallmark of cancer.⁵ Local and systemic inflammation is an important promoter of tumorigenesis, tumor cell proliferation, invasion, and metastasis, and it is also involved in the responsiveness to treatment agents.^{18,19} Tumor-induced inflammation can lead to peripheral hematological changes, including the changes of neutrophil, lymphocyte, monocyte and platelet, via the secretion of various kinds of cytokines.²⁰ Neutrophil is an indicator of acute and chronic inflammation, and

increasing evidences have shown that it can facilitate tumor cell proliferation, metastasis and evading immune surveillance by inhibiting T cell function, secreting immune suppressive factors including transforming growth factor-β, and inducing angiogenesis.²¹ Lymphocyte is the major mediator of host anti-tumor immunity, and leucopenia has been proven to be an adverse factor of patient prognosis.²² Monocyte, especially tumor associated macrophages (TAM), which is derived from circulating monocyte, could promote tumor progression by influencing tumor microenvironment.²³ Platelet is important mediator of coagulation, and it can promote tumor cell proliferation and angiogenesis by secreting growth factors and other cytokines.²⁴ Hence, blood cell counts are easy-to-get and cost-effective indexes to present host immune inflammation statuses, and there is increasing evidence showing that blood-based inflammatory markers, including NLR, PLR, and LMR,^{25–28} could be used as an effective marker in patients’ prognosis in various kinds of tumors.

SIRI is a novel index with a combination of neutrophil, lymphocyte, and monocyte counts, which is firstly

Table 3 Univariate Analysis of Potential Factors Associated with PFS and OS

Variables	PFS			OS		
	Case	MST(m)	P	Case	MST(m)	P
Age						
<65	177	14.8(12.7–15.3)	0.279	177	25.2(22.5–27.5)	0.264
≥65	68	14.3(11.4–16.6)		68	26.8(22.3–31.7)	
Gender						
Male	107	11.6(10.7–13.3)	0.057	107	28.2(25.9–30.1)	0.010
Female	138	14.4(12.8–15.2)		138	24.1(20.8–27.2)	
Smoking status						
No	176	14.2(12.3–15.7)	0.052	176	27.4(23.7–30.3)	0.084
Yes	69	11.7(10.6–13.4)		69	23.8(22.7–25.3)	
ECOG PS						
0–1	204	14.4(12.4–15.6)	0.007	204	28.3(25.7–30.3)	<0.001
2	41	10.7(9.3–12.7)		41	18.6(16.3–21.7)	
Brain metastasis						
Yes	26	11.1(9.4–12.6)	0.043	26	22.8(19.1–26.9)	0.038
No	219	14.4(12.4–15.6)		219	26.2(23.7–28.3)	
EGFR mutation						
L858R	101	11.9(10.1–13.9)	0.590	101	24.1(17.7–30.3)	0.829
19-DEL	134	14.4(12.0–16.0)		134	25.6(23.0–27.0)	
Other	10	12.0(NR)		10	25.2(NR)	
NLR						
<3.36	135	14.8(13.6–16.4)	0.128	135	27.8(26.1–29.9)	0.004
≥3.36	110	11.7(10.8–13.2)		110	21.7(19.4–24.6)	
PLR						
<167.01	123	14.3(11.7–16.3)	0.268	123	26.8(23.5–30.5)	0.281
≥167.01	122	11.8(10.6–13.4)		122	23.9(21.4–26.6)	
SIRI						
<0.71	54	16.4(NR)	0.002	54	NR	0.001
≥0.71	191	11.6(10.7–13.3)		191	23.8(21.7–26.3)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SIRI, systemic immune response index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; OS, overall survival; PFS, progression-free survival; MST, mean survival time.

reported by Qi et al²⁹ to be an effective prognosis factor in pancreatic cancer patients. Hence, SIRI has been proven to be an effective marker in predicting patients' survival in various kinds of cancers, including hepatocellular carcinoma,³⁰ gastric adenocarcinoma,³¹ nasopharyngeal carcinoma,³² esophageal squamous cell carcinoma,³³ breast cancer,³⁴ and cervical cancer.¹⁵ The research on the prognostic effect of SIRI on lung cancer patient is rare. Li et al¹⁶ reported that SIRI is an independent prognostic factor in lung cancer patients after thoroscopic surgery. However, the prognostic role of SIRI in advanced stage lung cancer patient remains unclear. In the present study, we demonstrated that

SIRI is an independent prognostic factor of advanced stage EGFR-mutant lung adenocarcinoma patients treated with EGFR-TKIs. However, in the present cohort of patients, only NLR is an independent prognostic factor of OS, while PLR was not a prognostic factor, which is not in accordance with previous studies.^{35,36} This may be due to the different cut-off value and different patient characteristics in different researches. Besides SIRI, we found that ECOG PS was also an independent prognostic factor, and patients with worse ECOG PS are more likely to have high level of NLR, PLR and SIRI, which indicated that systemic inflammation may be a reason of deterioration of general condition and drug resistance.

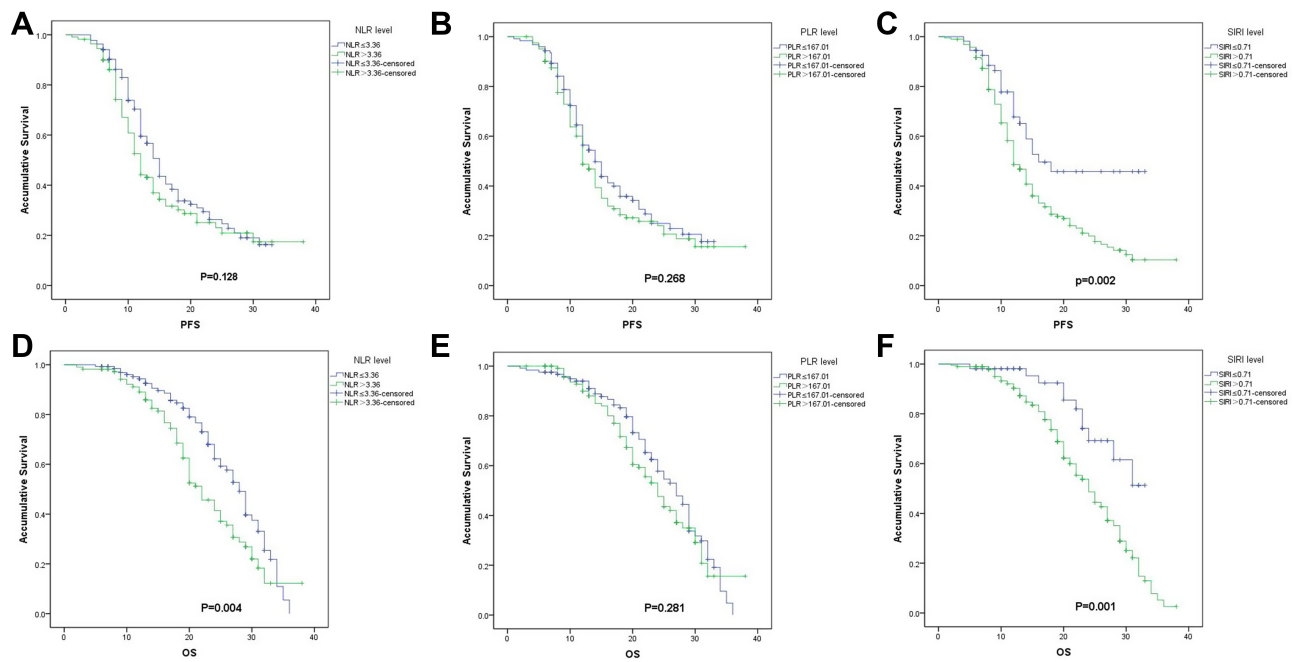


Figure 1 Kaplan–Meier survival curves for progression-free survival (PFS) according to NLR (A), PLR (B), and SRI (C), and overall survival (OS) according to NLR (D), PLR (E) and SRI (F) in EGFR-mutant lung adenocarcinoma patients treated with first-generation EGFR-TKIs.
Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SRI, systemic inflammation response index.

Although our research, together with previous researches, demonstrated that SIRI is a promising tool for predicting prognosis in lung adenocarcinoma patients, the results of our research should be interpreted with

cautious due to the obvious limitation of the research. First, the retrospective nature of the study, the same as that of most previous researches, will inevitably bring bias, such as patient selection bias and follow-up bias, to the

Table 4 Multivariable Cox Regression Analyses for PFS and OS

Variables	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
ECOG PS 0–1 2	2.562(1.667–3.940)	<0.001	2.431(1.571–3.761)	<0.001
Brain metastasis Yes No	1.630(0.980–2.711)	0.060	1.495(0.886–2.525)	0.132
Gender Female Male			1.206(0.825–1.761)	0.333
NLR ≥3.36 <3.36			1.275 (0.860–1.867)	0.212
SIRI ≥0.71 <0.71	2.384(1.275–4.459)	0.007	1.721 (1.024–3.898)	0.042

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SIRI, systemic immune response index; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

results. Second, due to the limited sample size, no validation cohort was established, which impaired the external authenticity of the result.

In summary, SIRI may be a convenient, cost-effective, and reliable marker for predicting prognosis in advanced lung adenocarcinoma patients treated with EGFR-TKIs. And it may help treatment adjustment and patient stratification. However, well-designed prospective trial is needed to further verify the results and the underlying mechanism of systemic inflammation induced EGFR-TKI resistance and early intervention modality worth further investigation.

Disclosure

The authors report no conflicts of interest in this work.

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