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The peripheral blood neutrophil-to-lymphocyte ratio is a prognostic predictor for survival of *EGFR*-mutant nonsmall cell lung cancer patients treated with EGFR-TKIs

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Abstract

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are the standard first-line treatment for EGFR-mutant nonsmall cell lung cancer (NSCLC) patients. However, studies have reported that not all NSCLC patients harboring kinase domain mutations in epidermal growth factor receptor (EGFR) show significant clinical benefits from EGFR-targeted tyrosine kinase inhibitors (TKIs). Therefore, it is necessary to establish feasible biomarkers to predict the prognosis of *EGFR*-mutant NSCLC patients treated with EGFR-TKIs. This study aimed to determine biomarkers using inflammatory parameters from complete blood counts to predict the prognosis of *EGFR*-mutant NSCLC patients treated with EGFR-TKIs.

We retrospectively investigated 127 stage IIIB/IV NSCLC patients with activating *EGFR* mutations who were treated with EGFR-TKIs. We used receiver operating characteristic (ROC) curves to determine the optimal cut-off for the inflammatory markers as prognostic factors. Additionally, univariate and multivariate analyses were used to identify prognostic factors for progression-free survival (PFS) and overall survival (OS) of *EGFR*-mutant NSCLC patients treated with EGFR-TKIs.

The receiver operating characteristic analysis indicated that the lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) cut-off values were 3.37 and 2.90, respectively. The univariate analysis showed that a high LMR (>3.37) and low NLR (≤2.90) were significantly correlated with long-term PFS and OS (LMR, $P = .007$; NLR, $P < .001$). The multivariate Cox regression analysis revealed that only low NLR was an independent prognostic factor for long-term PFS and OS (PFS, HR = 0.573, 95% CI: 0.340–0.964, $P = .036$; OS, HR = 0.491, 95% CI: 0.262–0.920, $P = .026$).

The data show that a low NLR was a good prognostic factor in *EGFR*-mutant NSCLC patients receiving EGFR-TKIs treatment. Moreover, the NLR measurement has better prognostic value than LMR.

Abbreviations: ARMS = amplification refractory mutation system, CBC = complete blood count, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, EDTA = ethylene diamine tetraacetic acid, EGFR = epidermal growth factor receptor, EGFR-TKIs = epidermal growth factor receptor-tyrosine kinase inhibitors, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, NSCLC = nonsmall cell lung cancer, OS = overall survival, PET-CT = position emission tomography computed tomography, PFS = progression-free survival, PLR = platelet-to-lymphocyte ratio, PS = performance status, RDW = red cell distribution width, RECIST = response evaluation criteria in solid tumors, ROC = receiver operating characteristic, TAMs = tumor associated macrophages, TANs = tumor-associated neutrophils, TILs = tumor infiltrating lymphocytes, TKIs = tyrosine kinase inhibitors, TME = tumor microenvironment.

Keywords: epidermal growth factor receptor, lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, nonsmall cell lung cancer, tyrosine kinase inhibitors

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1. Introduction

Lung cancer is one of most aggressive tumors and is a leading cause of cancer death worldwide.[1] Nonsmall cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, and approximately 70% of patients with NSCLC are initially diagnosed with advanced stage disease, which results in poor prognosis.[2] The epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib are part of a new treatment strategy for NSCLC patients with *EGFR* mutations and have improved the progression-free survival (PFS), overall survival (OS), and quality of life in patients compared to traditional platinum-based combination chemotherapy.[3–6] Epidermal growth factor receptor (EGFR) gene-activating mutations are strong predictive factors of response and survival to EGFR-TKIs.[7,8] It is generally accepted that 2 classical mutations (exon 19-del and exon 21-L858R) can enhance the sensitivity of tumor cells to EGFR-TKIs and are considered to be an effective predictor of the efficacy of EGFR-TKIs.[9] However, not all *EGFR*-mutated patients with nonsmall cell lung cancer show benefits from EGFR-TKIs. Although some patients benefit from EGFR-TKIs for more than 2 years, 20% to 30% of NSCLC cases have intrinsic or primary resistance to EGFR-TKIs despite harboring an activating *EGFR* mutation.[10] Therefore, it is critical to elucidate the factors influencing EGFR-TKIs response and establish feasible biomarkers to predict the efficacy of EGFR-TKIs.

Previous studies have investigated response biomarkers that can predict the prognosis of EGFR-TKIs efficacy using the next generation sequencing and other molecular analyses. However, these tests are expensive and difficult to perform and are impractical as routine exams. Thus, finding an effective way to evaluate the efficacy of EGFR-TKIs using routine clinical laboratory tests during tumor therapy will benefit advanced NSCLC patients.

Several recent studies evaluating the relationship between the immune system and tumors showed that the immune system plays important roles in killing tumor cells and preventing tumor growth while also providing an inflammatory microenvironment that fosters tumor growth via a process called immunoediting.[11,12] It has been reported that the immune response profile and inflammatory signature in several cancers may provide useful information on patient prognosis and treatment.[13,14]

Complete blood count (CBC) is one of the most common laboratory tests performed in the clinic. The absolute count of neutrophils, lymphocytes, and monocytes reflects the inflammatory response and overall immune status of the body. Peripheral blood prognostic inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and red cell distribution width (RDW) are associated with patient prognosis and treatment outcome.[15–18] However, there are a limited number of reports about the relationship between these inflammatory markers and the efficacy of EGFR-TKIs in advanced NSCLC patients with *EGFR* mutations.

In this study, we conducted a retrospective analysis to assess the value of the inflammatory parameters obtained from CBCs in predicting the prognosis in *EGFR*-mutant NSCLC patients treated with EGFR-TKIs. Our results indicated NLR as an independent prognostic biomarker for PFS and OS in NSCLC patients with *EGFR* mutations following EGFR-TKIs treatment.

2. Materials and methods

2.1. Patient and clinical characteristics

This study was approved by the institutional research ethics board. We retrospectively analyzed the clinical data of NSCLC patients at the Affiliated Tumor Hospital of Xinjiang Medical University between January 2013 and December 2015. The patients were followed-up until July 2017. The following inclusion criteria were used: adult patient aged 18 years or older; histologically or cytologically confirmed NSCLC; clinical stage IIIB or IV; harbor activating *EGFR* mutation (exon 19-del and exon 21 L858R); at least one evaluation of lesions according to the response evaluation criteria in solid tumors (RECIST); Eastern Cooperative Oncology Group (ECOG) performance status between 0 to 4; and treatment with EGFR-TKI as a first-line cancer therapy. The study exclusion criteria were the following: patients with other malignancies, infection, or hematological or autoimmune diseases; patients who are allergic and/or intolerant to EGFR-TKIs.

The following patient clinical characteristics were obtained: general condition, medical history, tumor pathology, ECOG performance status, *EGFR* mutation type, treatment history, laboratory values, and imaging data.

2.2. Treatment and monitoring methods

Patients received gefitinib (250 mg/day) or erlotinib (150 mg/day) until detection of progressive disease or intolerable toxicity. We obtained informed consent from all patients prior to treatment.

The patient disease baseline status was assessed 2 weeks prior to the initiation of EGFR-TKIs treatment. The disease assessments including clinical parameters, hematological parameters, biochemistry, tumor markers and chest radiography were performed every 4 weeks. The chest computed tomography (CT) or position emission tomography computed tomography (PET-CT) was performed every 2 to 3 months. Disease progression was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).[19] The survival indicators for progression-free survival (PFS) are defined as the time from the initiation of EGFR-TKIs to disease progression, death before documented progression, or the last follow-up time. The patient overall survival (OS) is defined as the time from the initiation of EGFR-TKIs to death or last follow-up.

2.3. Sample collection

Venous blood samples were collected in ethylene diamine tetraacetic acid (EDTA) anticoagulant tubes. The tumor tissues were mainly obtained from CT-guided biopsies and were then fixed with 10% buffered formalin and embedded in paraffin. The blood samples and tissues were collected no >7 days before initiating EGFR-TKIs treatment.

2.4. EGFR mutation testing

Genomic DNA was extracted from 5 sections of 10 μm thickness using the QIAamp DNA FFPE Tissue kit (Qiagen, Hilden, Germany). *EGFR* mutations were tested by an amplification refractory mutation system (ARMS) using the ADx-ARMS *EGFR* mutation test kit (Amoy Diagnostics, Xiamen, China) according to manufacturer's instructions.

2.5. Complete blood count (CBC) testing

The CBC with differential was tested by the automated hematology analyzer Sysmex XE-5000. The laboratory information collected from the CBC included the white blood cell count, absolute neutrophil, monocyte and lymphocyte counts, platelet counts and red cell distribution width (RDW). The peripheral LMR was calculated as the ratio of peripheral lymphocytes to monocytes. The peripheral NLR and PLR were calculated as the ratio of the neutrophils and platelets to lymphocytes.

2.6. Statistical analysis

The clinical characteristics of the patients were analyzed by descriptive statistics. Pearson's chi-square test, Fisher's exact test, or Student's *t* test was used to compare the baseline clinical characteristics between different groups as applicable. The receiver operating characteristic (ROC) curves and Youden's index were utilized to determine the optimal cut-off for the inflammatory markers (white blood cell count, absolute neutrophil, monocyte and lymphocyte counts, platelet counts, and red cell distribution width) as prognostic factors. The univariate analysis of PFS and OS outcomes in the study groups was performed using the Kaplan–Meier method and the log-rank test. A multivariate Cox proportional hazard model was used to further identify independent prognostic factors for PFS and OS. All statistical assessments were 2-sided. All results with *P*-values <0.05 were considered statistically significant. All analyses were performed using SPSS software (version 19.0., SPSS Inc., Chicago).

3. Results

3.1. Patient characteristics

There were 1371 stage IIIB/IV NSCLC patients with *EGFR* mutation testing results. Among these patients, 575 patients harbored activating *EGFR* mutations of either an exon 19 microdeletion or exon 21 point mutation (L858R). There were 227 patients treated with first-line EGFR-TKIs (gefitinib or erlotinib). There were 40 excluded patients who stopped EGFR-TKIs treatment before disease progression and 54 patients who were lost to follow-up. There were 6 patients who had no laboratory data before EGFR-TKI treatment. Thus, there were 127 patients enrolled in the final analysis (Fig. 1). The patient demographic and baseline characteristics are shown in Table 1. The mean age of the study population was 61.9 years. After a mean follow-up time of 28.12 months (range, 3–49), there were 108 patients who experienced disease progression, and 69 patients died. The median PFS was 11.0 months, and the median OS was 18.0 months. The median counts of neutrophils, lymphocytes, monocytes, and platelets were 4.34×10^9 cells/L (range, 1.17–11.02 $\times 10^9$ cells/L), 1.45×10^9 cells/L (range, 0.27–3.85 $\times 10^9$ cells/L), 0.43×10^9 cells/L (range, 0.03–1.28 $\times 10^9$ cells/L), and 232.00×10^9 cells/L (range, 68–518 $\times 10^9$ cells/L), respectively. The median NLR, LMR, PLR, and RDW were 2.98 (range, 0.62–29.53), 3.53 (range, 0.63–79.00), 164.44 (range, 48.76–618.52) and 13.7 (range, 11.40–19.90), respectively.

3.2. Determination of the best immunologic parameter cut-off values

We used PFS longer or shorter than 10 months as the binary variable for receiver operating characteristic (ROC) curves.

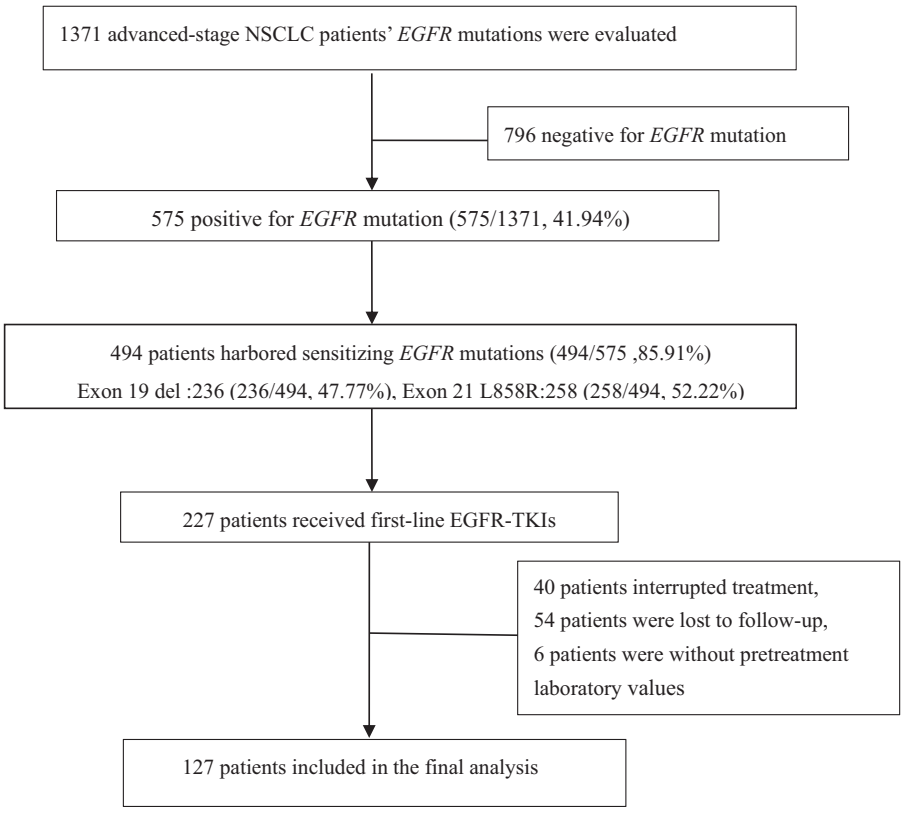

Figure 1. Flowchart for selecting patients.

Table 1

Clinical characteristics and therapy responses of 127 *EGFR* mutant NSCLC patients.

Characteristics	Data (n = 127)
Age, years	
≤65	84 (66.14%)
>65	43 (33.86%)
Gender	
Female	72 (56.69%)
Male	55 (43.31%)
Smoking history	
Nonsmoker	91 (71.65%)
Smoker	36 (28.35%)
Histology	
Adenocarcinoma	117 (92.13%)
Squamous	10 (7.87%)
Stage	
IIIB	26 (20.47%)
IV	101 (79.53%)
ECOG PS	
ECOG 0-1	76 (59.84%)
ECOG 2-4	51 (40.16%)
EGFR-TKIs	
Erlotinib	45 (35.43%)
Gefitinib	82 (64.57%)
EGFR mutation	
Exon 19 del	78 (61.42%)
Exon 21 L858R	49 (38.58%)
Neutrophil count (median ± IQR × 10^9/L)	4.34 ± 3.00
Lymphocyte count (median ± IQR × 10^9/L)	1.45 ± 0.69
Monocyte count(median ± IQR × 10^9/L)	0.43 ± 0.21
Platelet count (median ± IQR × 10^9/L)	232.00 ± 92.00
LMR (median ± IQR)	3.53 ± 2.40
NLR (median ± IQR)	2.98 ± 2.19
PLR (median ± IQR)	164.44 ± 93.33
RDW (median ± IQR)	13.70 ± 2.30
PFS (median), months	11.0
OS (median), months	18.0

ECOG = Eastern Cooperative Oncology Group, EGFR-TKIs = Epidermal growth factor receptor-tyrosine kinase inhibitors, IQR = inter quartile range, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte, OS = overall survival, PFS = progression-free survival, PLR = Platelet–to- lymphocyte ratio, PS = performance status, RDW = red cell distribution width.

According to the highest Youden index (specificity+sensitivity–1), the optimal cut-off value chosen for the LMR was 3.37, with an area under the curve (AUC) value of 0.652 [95% confidence interval (CI), 0.557–0.747, $P = .003$] (Fig. 2A). The most discriminating cut-off value of NLR was 2.90, with an area under the curve (AUC) value of 0.668 [95% confidence interval (CI), 0.572–0.764, $P = .001$] (Fig. 2B). However, we did not identify significant cut-off values for the PLR and RDW. In a subsequent analysis all patients' LMR and NLR were divided into high-level and low-level groups according to the optimal cutoff values.

3.3. Correlation of NSCLC patients' characteristics with the LMR and NLR The univariate analysis between clinical factors

The baseline characteristics of the NSCLC patients according to the NLR and the LMR are listed in Table 2. We analyzed the correlation of the baseline characteristics for the NSCLC patients and the LMR and NLR. The results showed that there was no significant difference regarding the patient's age, smoking history, histology, stage, ECOG performance status, EGFR-TKIs, or *EGFR* mutations between 2 groups of high-level and low-level LMR. However, female NSCLC patients ($P = .013$), decreased neutrophil count ($P = .002$), increased lymphocyte count ($P < .001$), and decreased monocyte count ($P < .001$) were significantly associated with high-level LMR.

There was no significant difference identified regarding patient's age, gender, smoking history, histology, stage, ECOG performance status, EGFR-TKIs, or *EGFR* mutation between the high-level and low-level NLR groups. However, increased neutrophil count ($P < .001$), decreased lymphocyte count ($P < .001$) and increased monocyte count ($P = .001$) were significantly associated with high-level NLR.

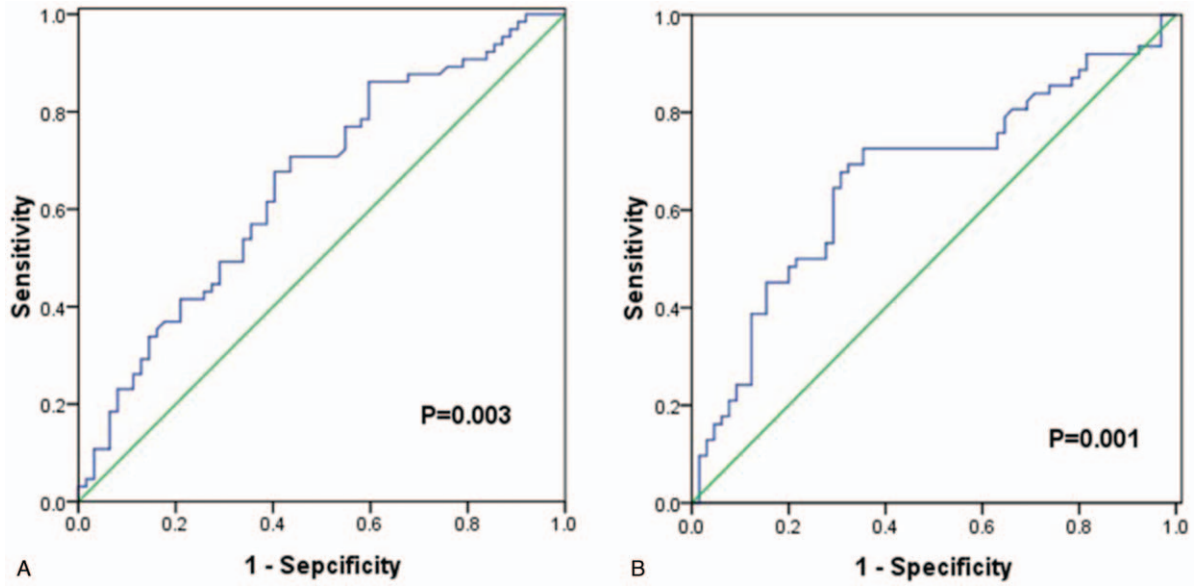

Figure 2. Receiver operating characteristic (ROC) curves analysis for lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) in enrolled non-small cell lung cancer patients. (A) ROC curve analysis for LMR in enrolled nonsmall cell lung cancer patients. (B) ROC curves analysis for neutrophil-to-lymphocyte ratio (NLR) in enrolled nonsmall cell lung cancer patients. LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte, ROC = receiver operating characteristic.

Table 2

The associations between inflammatory marks and clinical features.

Characteristics	n	LMR≤3.37	LMR>3.37	*P* value	NLR≤2.90	NLR>2.90	*P* value
Age				.206			.213
≤65	84	35	49		43	41	
>65	43	23	20		17	26	
Gender				.013			.153
Female	72	26	46		38	34	
Male	55	32	23		22	33	
Smoking history				.335			.696
Nonsmoker	91	44	47		42	49	
Smoker	36	14	22		18	18	
Histology				.109			.515
Adenocarcinoma	117	56	61		54	63	
Squamous	10	2	8		6	4	
Stage				.700			.058
IIIB	26	11	15		12	28	
IV	101	47	54		48	53	
ECOG PS				.797			.027
ECOG 0-1	76	34	42		42	34	
ECOG 2-4	51	24	27		18	33	
EGFR-TKIs				.837			.640
Erlotinib	45	20	25		20	25	
Gefitinib	82	38	44		40	42	
EGFR mutation				.384			.499
Exon 19 del	78	38	40		35	43	
Exon 21 L858R	49	20	29		25	24	
Neutrophil count (10^9/L)	127	5.459±2.529	4.191±1.954	.002	3.383±1.466	6.013±2.232	<.001
Lymphocyte count (10^9/L)	127	1.167±0.428	1.807±0.612	<.001	1.793±0.640	1.266±0.489	<.001
Monocyte count (10^9/L)	127	0.551±0.233	0.360±0.142	<.001	0.381±0.157	0.506±0.235	.001

ECOG = Eastern Cooperative Oncology Group, EGFR-TKIs = Epidermal growth factor receptor-tyrosine kinase inhibitors, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte, PS = performance status.

3.4. Association between clinical factors of NSCLC patients and survival

We subsequently investigated the association between clinical factors of NSCLC patients and survival in the univariate analysis and multivariate Cox regression analysis.

The univariate analysis between clinical factors, inflammatory markers, and PFS showed that a longer PFS duration was significantly correlated with low ECOG PS (ECOG 0-1) ($P<.001$), high LMR ($P=.007$) (Fig. 3A) and low NLR ($P<.001$) (Fig. 3B). However, age, gender, history of smoking, type of histology, EGFR-TKIs, and *EGFR* mutation had no significant influence on PFS (Table 3). The multivariate Cox regression analysis revealed that the independent predictive factors for longer PFS were low ECOG PS (hazard ratio 0.467, 95% confidence interval: 0.299–0.731, $P=.001$), exon 19 del (hazard ratio 0.507, 95% confidence interval: 0.327–0.786, $P=.002$) and low NLR (hazard ratio 0.573, 95% confidence interval: 0.340–0.964, $P=.036$) (Table 4).

In the univariate analysis, there were significant correlations between longer OS and low ECOG PS ($P=.002$), high LMR ($P=.034$) (Fig. 3C), and low NLR ($P<.001$) (Fig. 3D). OS duration had no significant correlation with age, gender, history of smoking, type of histology, EGFR-TKIs, or *EGFR* mutation (Table 3). However, the Cox proportional multivariate hazard model revealed that low ECOG PS (hazard ratio 0.495, 95% confidence interval: 0.291–0.845, $P=.010$) and low NLR (hazard ratio 0.491, 95% confidence interval: 0.262–0.920, $P=.026$) were independent prognostic factors correlated with longer OS (Table 4).

4. Discussion

The analysis of prognostic factors affecting tumor therapy can facilitate the use of an optimal management strategy. In this retrospective study, we investigated the prognostic values of inflammatory parameters from CBC and other clinical factors in NSCLC patients with *EGFR* mutations treated with EGFR-TKIs. Our results demonstrated that decreased NLR and increased LMR were significantly associated with longer survival, PFS and OS in *EGFR*-mutant NSCLC patients following treatment with EGFR-TKIs. However, the multivariate analysis Cox model indicated that only the NLR remained an independent significant predictor of PFS and OS. The LMR had no prognostic significance for NSCLC patient survival. It is possible that the strong predictive ability of NLR affected the predicative function of LMR in our multivariate analysis. Thus, NLR was superior to LMR in the prognosis of *EGFR*-mutant NSCLC patients treated with EGFR-TKIs.

It has been shown that the tumor microenvironment (TME) orchestrates tumorigenesis and malignant progression. The TME significantly influences both tumor therapeutic response and its efficacy.[20] Additionally, tumor-associated neutrophils (TANs), tumor infiltrating lymphocytes (TILs), and tumor associated macrophages (TAMs) are important components of the TME and regulate the inflammatory response. These cells have also been identified as prognostic factors in malignant tumors including NSCLC.[21,22] The TANs in pretreatment peripheral blood are correlated with high-grade invasive histologic subtypes of lung adenocarcinomas and were identified as an independent prognostic factor using large cohorts of patients with advanced NSCLC.[23,24] NSCLC patients with high levels of $CD3^+$ TILs in

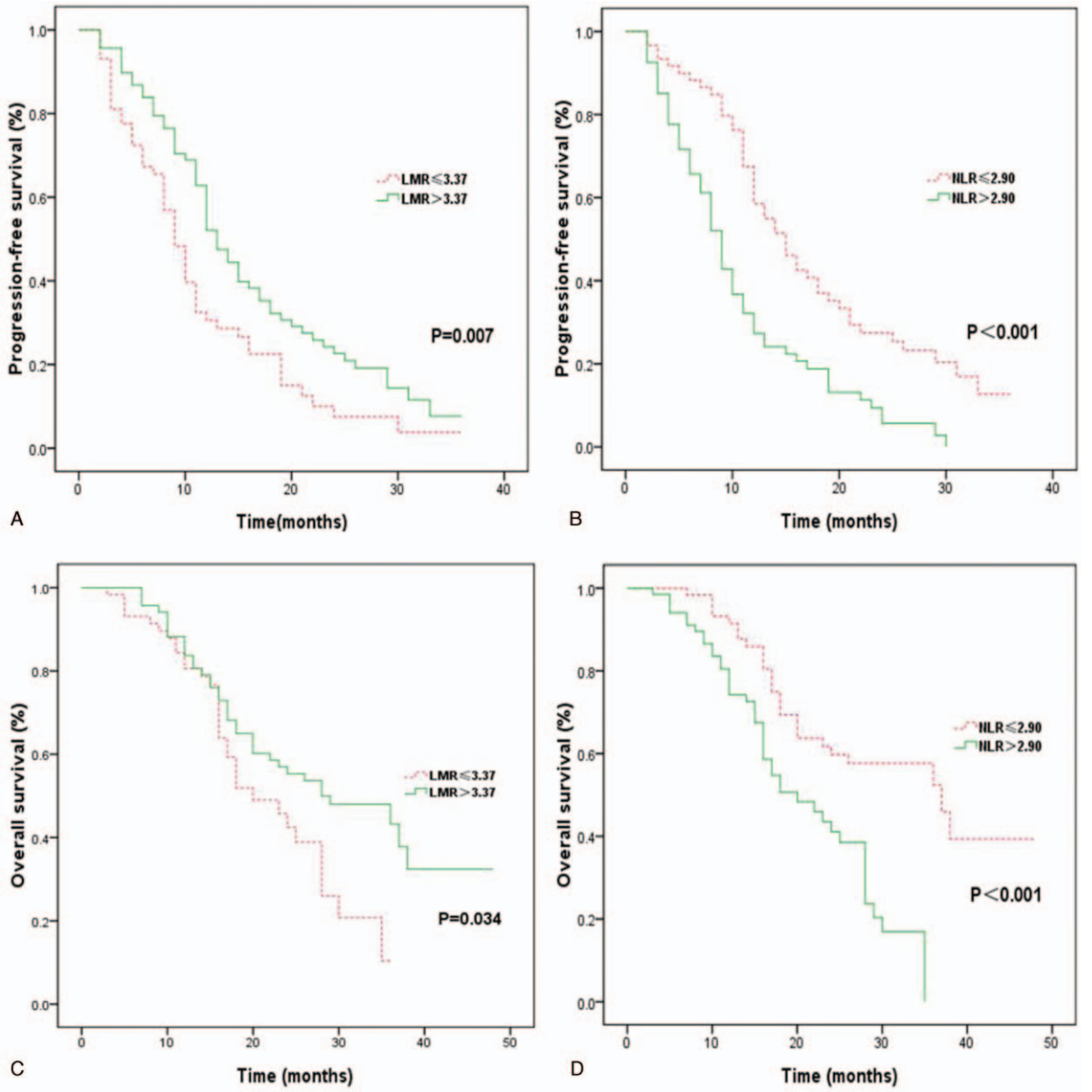

Figure 3. Kaplan–Meier curves for *EGFR* mutant non-small cell lung cancer patients treated with epidermal growth factor receptor-tyrosine kinase inhibitors. (A) PFS between high and low baseline lymphocyte-to-monocyte ratio (LMR) patients; (B) PFS between high and low neutrophil-to-lymphocyte ratio (NLR) patients; (C) OS between high and low baseline LMR patients; (D) OS between high and low baseline NLR patients. LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte, OS = overall survival, PFS = progression-free survival.

tumor lesions and IL-2-expressing tumors had significantly better 5-year OS rates.[25] It has also been shown that low PD-L1 expression in $CD8^+$ TILs is associated with longer PFS and OS in NSCLC patients.[22] High TAM infiltration is closely related to drug resistance and poor prognosis in various cancers including NSCLC.[26,27] In addition, high TAMs were significantly related to poor progression-free survival and overall survival in *EGFR*-mutant NSCLC patients.[28,29]

Several recent clinical studies indicated the lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) in pretreatment peripheral blood had significant prognostic values in patients with malignant tumors.[30–33] Jia et al[34] showed the LMR and NLR were significantly associated with survival of triple-negative breast cancer patients, but the neutrophil, lymphocyte and monocyte counts alone were not associated. Our results also indicate low LMR and high NLR were significantly associated with short-term PFS and OS in *EGFR*-mutant NSCLC patients treated with EGFR-TKIs. Recently, Chen et al[35] reported that baseline and LMR trends were prognostic factors in *EGFR*-mutant NSCLC patients treated with EGFR-TKIs. However, other studies reported that low NLR values were strongly correlated with better PFS and OS in *EGFR*-mutated NSCLC patients receiving EGFR-TKIs.[36] In our studies, we found that both LMR and NLR were significantly correlated with the survival of *EGFR*-mutant NSCLC patients in the univariate analysis. Moreover, the multivariate Cox regression analysis found that high NLR was superior to low LMR as an independent significant predictor of long-term PFS and OS in *EGFR*-mutant NSCLC patients treated with EGFR-TKIs.

Table 3

Univariate analysis of prognostic factors for progression-free survival and overall survival in 127 NSCLC patients with *EGFR* mutations.

Characteristics	n (127)	Progression-free survival		Overall survival	
		Median, months	*P* value	Median, months	*P* value
Age			.935		.561
≤65	84	13.948		27.224	
>65	43	14.465		28.329	
Gender			.238		.559
Female	72	14.862		26.860	
Male	55	12.921		26.658	
Smoking history			.774		.465
Nonsmoker	91	14.154		27.851	
Smoker	36	13.621		26.425	
Histology			.703		.828
Adenocarcinoma	117	13.902		27.277	
Squamous	10	15.300		28.780	
Stage			.356		.586
IIIB	26	15.690		27.556	
IV	101	13.572		27.304	
ECOG PS			<.001		.002
ECOG 0-1	76	16.501		30.632	
ECOG 2-4	51	10.065		20.935	
EGFR-TKIs			.242		.444
Erlotinib	45	12.475		25.651	
Gefitinib	82	14.765		28.031	
EGFR mutation			.204		.741
Exon 19 del	78	14.886		28.025	
Exon 21 L858R	49	12.536		26.760	
LMR			.007		.034
≤3.37	58	11.460		21.905	
>3.37	69	16.125		29.978	
NLR			<.001		<.001
≤2.90	60	17.740		32.667	
>2.90	67	10.646		20.910	

ECOG = Eastern Cooperative Oncology Group, EGFR-TKIs = Epidermal growth factor receptor-tyrosine kinase inhibitors, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte, PS = performance status.

Our study results suggest that *EGFR*-mutant NSCLC patients with high NLR levels at baseline might have poor survival outcomes if simply treated with EGFR-TKIs. For these NSCLC patients, alternating or combination chemotherapy strategies with EGFR-TKIs may achieve ideal therapeutic effects. However, further clinical studies are required. The major limitation of our research is that it is a retrospective study. Therefore, we could not control for underlying positive or negative biases during the treatment or selection of patients in our analysis. There are also limitations due to its single-institute retrospective design. Thus, we believe that it is important to validate these data in future multicenter prospective studies.

5. Conclusions

The NLR and LMR are reliable and convenient biomarkers for predicting the outcomes of NSCLC patients with *EGFR* mutations who were treated with EGFR-TKIs. The high LMR

Table 4

Multivariate Cox proportional regression analyses of prognostic factors for progression-free survival and overall survival.

Characteristics	Progression-free survival			Overall survival		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (≤65 vs >65)	1.353	0.879–2.084	.170	1.389	0.817–2.361	.225
Gender (female vs male)	0.994	0.651–1.517	.977	0.780	0.444–1.370	.387
Smoking (yes vs no)	0.744	0.476–1.163	.195	0.717	0.418–1.230	.227
Histology (adenocarcinoma vs squamous)	0.809	0.371–1.762	.593	0.898	0.373–2.163	.811
Stage (IIIB vs IV)	0.857	0.518–1.417	.547	0.909	0.503–1.645	.754
ECOG PS (0–1 vs 2–4)	0.467	0.299–0.731	.001	0.495	0.291–0.845	.010
EGFR-TKIs (Erlotinib vs Gefitinib)	1.243	0.804–1.921	.327	1.152	0.665–1.995	.614
EGFR mutation (Exon 19 del vs Exon 21 L858R)	0.507	0.327–0.786	.002	0.656	0.386–1.114	.119
LMR (≤3.37 vs >3.37)	1.575	0.926–2.677	.093	1.422	0.766–2.640	.265
NLR (≤2.90 vs >2.90)	0.573	0.340–0.964	.036	0.491	0.262–0.920	.026

ECOG = Eastern Cooperative Oncology Group, EGFR-TKIs = Epidermal growth factor receptor-tyrosine kinase inhibitors, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte, PS = performance status.

and low NLR were significantly associated with better PFS and OS in the univariate analysis. The multivariate analysis indicated that low NLR is an independent prognostic biomarker for long-term PFS and OS and is superior to high LMR in advanced NSCLC patients after EGFR-TKI treatment. The NLR was directly derived from CBC data and can be easily applied in clinical practice.

Author contributions

Data curation: Yuan Zhang, Yang-Chun Feng, Hong-Ge Zhu, Jia Song.
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