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, \(P = 0.007; \) NLR, \(P < 0.001\)). 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, \(P = 0.036\); OS, HR = 0.491, 95% CI: 0.262–0.920, \(P = 0.026\)).

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 the 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 immuno-editing. [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 NSCL; 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 × 10⁹ cells/L (range, 1.17–11.02 × 10⁹ cells/L), 1.45 × 10⁹ cells/L (range, 0.27–3.85 × 10⁹ cells/L), 0.43 × 10⁹ cells/L (range, 0.03–1.28 × 10⁹ cells/L), and 232.00 × 10⁹ cells/L (range, 68–518 × 10⁹ 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.
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 < .001), 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.

### Table 1

| Characteristics | Data (n = 127) |
|-----------------|---------------|
| Age, years | 84 (66.14%)<br>43 (33.86%) |
| Gender | Female 72 (56.69%)<br>Male 55 (43.31%) |
| Smoking history | Non-smoker 91 (71.65%)<br>Smoker 36 (28.35%) |
| Histology | Adenocarcinoma 117 (92.13%)<br>Squamous 10 (7.87%) |
| Stage | IIB 26 (20.47%)<br>V 101 (79.53%) |
| ECOG PS | ECOG 0-1 76 (60.84%)<br>ECOG 2-4 51 (40.16%) |
| EGFR-TKIs | Erlotinib 45 (35.43%)<br>Geftinib 82 (64.57%) |
| EGFR mutation | Exon 19 del 78 (61.42%)<br>Exon 21 L858R 49 (38.58%) |
| Neutrophil count (median±IQR × 10^3/L) | 4.34 ± 3.00 |
| Lymphocyte count (median±IQR × 10^3/L) | 1.45 ± 0.69 |
| Monocyte count (median±IQR × 10^3/L) | 0.43 ± 0.21 |
| Platelet count (median±IQR × 10^9/L) | 232.00 ± 92.00 |
| LMR (median±IQR) | 3.53 ± 2.19 |
| 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 ratio, PS = performance status, RDW = red cell distribution width.
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 associated with low smoking history (hazard ratio 0.467, 95% confidence interval: 0.327–0.696, P < 0.001) (Table 2). However, age, gender, history of smoking, type of histology, EGFR-TKIs, and LMR had no significant influence on PFS (Table 3). The multivariate Cox regression analysis revealed that smoking (P < 0.001) (Fig. 3A) and low LMR (P < 0.001) (Fig. 3B) had a strong predictive ability of NLR affected the predictive function for NSCLC patient survival. It is possible that the strong predictive ability of NLR affected the predictive function of OS and PFS. The LMR had no prognostic significance for NSCLC patient survival. It is possible that the strong predictive ability of NLR affected the predictive function of OS and PFS. The LMR had no prognostic significance for NSCLC patient survival. It is possible that the strong predictive ability of NLR affected the predictive function of OS and PFS. The LMR had no prognostic significance for NSCLC patient survival. It is possible that the strong predictive ability of NLR affected the predictive function of OS and PFS. The LMR had no prognostic significance for NSCLC patient survival. It is possible that the strong predictive ability of NLR affected the predictive function of OS and PFS. The LMR had no prognostic significance for NSCLC patient survival.

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 predictive function of OS and PFS.

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. 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. 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. NSCLC patients with high levels of CD3+ TILs in
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.\[10-33\] Jia et al\[33\] 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.

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.
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 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 | Median, months | P value | Overall survival | Median, months | P value |
| Age | 84 | <65 | 13.948 | .935 | 27.224 | .561 |
| | 43 | >65 | 14.465 | .238 | 28.329 | .559 |
| Gender | 72 | Female | 14.862 | .774 | 27.851 | .465 |
| | 55 | Male | 12.921 | | 26.680 | |
| Smoking history | 91 | Nonsmoker | 14.154 | | 27.851 | |
| | 36 | Smoker | 13.621 | | 26.425 | |
| Histology | | | | | | |
| | | | | | | |
| | | | | | | |
| Adenocarcinoma | 117 | 13.902 | | | 27.277 | |
| Squamous | 10 | 15.300 | | | 28.780 | |
| Stage | | IB | 15.690 | | 27.556 | |
| | | IB | 13.572 | | 27.304 | |
| | | ECOG PS | | | | |
| | | ECOG 0-1 | 16.501 | <.001 | 30.632 | .002 |
| | | ECOG 2-4 | 10.065 | | 20.935 | |
| | | EGFR-TKIs | | | | |
| | | Erlotinib | 12.475 | | 25.651 | |
| | | Gefitinib | 14.765 | | 28.031 | |
| | | EGFR mutation | | | | |
| | | Exon 19 del | 14.886 | | 28.025 | |
| | | Exon 21 L858R | 12.536 | | 26.760 | |
| | | LMR | | | | |
| | | ≤3.37 | 11.460 | .242 | 21.905 | .444 |
| | | >3.37 | 16.465 | | 29.978 | |
| | | NLR | | | | |
| | | ≤2.90 | 17.740 | <.001 | 32.667 | <.001 |
| | | >2.90 | 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
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

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