Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(12) 1–11

DOI: 10.1177/0300060520980205
journals.sagepub.com/home/imr
SAGE

Platelet/lymphocyte ratio is a significant prognostic factor for targeted therapy in patients with EGFR-mutated non-small-cell lung cancer

Kejun Liu[1,*], Guanming Jiang[1,*], Nianxin Fang[2,*], Limin Cai[1,†], Wei Du[3,†] and Jun Jia[1,†]

Abstract

Objective: To analyze the prognostic significance of the pretreatment platelet/lymphocyte ratio (PLR) for targeted therapy in patients with epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC).

Methods: We conducted a retrospective study of 96 patients with EGFR-mutated advanced NSCLC who were treated at Dongguan People's Hospital, Southern Medical University from May 2014 to December 2017. All patients received EGFR-targeted therapy until disease progression, unacceptable toxicity, or other factors. Approximately 3 days before the initial treatment, data including a detailed clinical history, physical examination, radiographic results, pathological diagnosis, and laboratory parameters including complete blood cell counts and albumin levels were evaluated.

[1]Dongguan Institute of Clinical Cancer Research, Dongguan People's Hospital, Southern Medical University, Dongguan, China
[2]Department of Pulmonary and Critical Care Medicine, Dongguan People's Hospital, Southern Medical University, Dongguan, China
[3]Department of Thoracic Surgery, Dongguan People's Hospital, Southern Medical University, Dongguan, China

*Kejun Liu, Guanming Jiang, and Nianxin Fang contributed equally to this work.

†Limin Cai, Wei Du and Jun Jia contributed equally to this work.

Corresponding authors:
Jun Jia, Dongguan Institute for Clinical Cancer Research, Dongguan People's Hospital, Southern Medical University, 3 Wandao Road South, Dongguan, Guangdong 523059, China.
Email: jiwen6465@126.com
Wei Du, Department of Thoracic Surgery, Dongguan People's Hospital, Southern Medical University, 3 Wandao Road South, Dongguan, Guangdong 523059, China.
Email: duwei1227@sina.com

Results: Patients in the PLR $\geq$ 190 group had shorter progression-free survival (PFS) than those in the PLR $<$ 190 group. Furthermore, the 1-year PFS rate was worse in the PLR $\geq$ 190 group than in the PLR$<$ 190 group. Multivariate analysis indicated the possible role of PLR as a prognostic factor for patients with advanced NSCLC who received EGFR-targeted therapy.
Conclusions: Pretreatment PLR may be an independent prognostic factor for patients with NSCLC receiving EGFR tyrosine kinase inhibitor treatment. Further studies are needed to identify the impact of PLR on EGFR-mutated NSCLC.

Keywords
Non-small-cell lung cancer, epidermal growth factor receptor, targeted therapy, platelet/lymphocyte ratio, prognostic factor, tyrosine kinase inhibitor, progression-free survival

Date received: 15 June 2020; accepted: 12 November 2020

Introduction

Lung cancer, the most frequent cancer diagnosed each year, is commonly classified as small-cell lung cancer or non-small-cell lung cancer (NSCLC).[1,2] NSCLC comprises approximately 80% of all lung cancers, and 40% to 50% of Asian patients harbor epidermal growth factor receptor (EGFR) mutations.[3–5] NSCLC is closely associated with inflammation and chronic infection.[6,7] The tumor microenvironment of lung cancer is composed of tumor cells, inflammatory cells, and fibroblasts, among others. It is postulated that tumor progression may be promoted by a variety of inflammatory factors, which may eventually affect chemotherapeutic efficacy.[8]

For patients treated with EGFR tyrosine kinase inhibitors (EGFR-TKIs), it is unknown whether inflammatory factors affect the antitumor efficacy of targeted drugs. To date, the EGFR mutation status remains an extremely powerful predictive factor. However, only some patients with EGRF-mutated cancer benefit from targeted therapy. Hence, other predictive factors are needed to complement the mutation status, such as biomarkers of systemic inflammatory responses.

Over the last decade, hematological inflammatory response markers such as the platelet/lymphocyte ratio (PLR) and C-reactive protein/albumin ratio (CAR) have been studied as prognostic factors in patients with various cancers.[9,10] Studies found that the T cell population is predominant in the tumor microenvironment compared with the abundance of other inflammatory cells such as natural killer cells. Tumor-infiltrating T cells in advanced lung cancer could cause malignancy-induced immunosuppression, which probably weakens the antitumor effect of targeted therapy for advanced NSCLC. In addition, several reports revealed that high baseline platelet counts were closely associated with shorter overall survival (OS) in patients with advanced NSCLC.[11,12] Although PLR has been extensively investigated in different tumor categories, few studies have examined the predictive relationship between PLR and the efficacy of EGFR-targeted therapy.

Therefore, we analyzed the predictive utility of PLR in patients with EGFR-mutated

NSCLC to verify our hypothesis regarding its prognostic role in such patients.

Patients and Methods

Patients

This was a retrospective study of patients with advanced NSCLC who received EGFR-targeted therapy at Dongguan People's Hospital, Southern Medical University from May 2014 to December 2017. The inclusion criteria were age $\geq$18 years, life expectancy of 4 weeks or more, adequate bone marrow function, a diagnosis of stage IIIB (with pleural effusion) or stage IV NSCLC (The International Association for the Study of Lung Cancer 7th edition of Tumor Node Metastasis Staging classification) harboring EGFR gene mutations, and no prior receipt of antitumor treatment. EGFR mutations were identified in tumor tissues using standard sequencing methods. Patients were excluded from the study if they met the following criteria: allergy to targeted therapies, primary organ failure, pregnancy, hematological or autoimmune disease, serious liver or kidney dysfunction, and missing follow-up data. The clinical data of the included patients were collected carefully. The present study was approved by the Ethics Committee of Dongguan People's Hospital (approval date, 16 November 2017), and the study was conducted according to the Declaration of Helsinki. Patients provided informed written consent.

Clinical management

All patients with advanced NSCLC in the study were treated with a standard dose of EGFR-TKIs, including gefitinib, erlotinib, and icotinib. Approximately 3 days before initial treatment, the following data were evaluated: detailed clinical history, physical examination, radiographic results, pathological diagnosis, and laboratory parameters including complete blood cell counts and albumin levels. Patients received targeted therapy daily until unendurable toxicity or disease progression occurred. All patients were followed for at least 6 months after the initiation of EGFR-TKI therapy. Computed tomography, radionuclide bone scan, and magnetic resonance imaging were conducted to evaluate treatment efficacy. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors. Disease control was defined as complete response, partial response (PR), stable disease (SD), or progression disease (PD). Toxicities were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA). We selected the cutoff for PLR using receiver operating characteristic (ROC) curve analysis. The associations of PLR with clinicopathological parameters were assessed via Pearson's chi-squared test. PFS was defined as the time from the start of the treatment to disease progression or death, with data censored for patients alive without progression at the last follow-up visit. The cutoff date for PFS data was 28 June 2018. By that time, sufficient data had been collected to analyze the efficacy and toxicities of targeted therapy. The objective response rate (ORR) and disease control rate (DCR) were also recorded. Estimates of PFS were calculated using the Kaplan–Meier method, and two-sided 95% confidence intervals (CIs) were obtained. A two-sided log-rank test was used to

compare PFS between different PLR groups. Prognostic analysis was conducted using univariate and multivariate Cox regressions models. Variables significant at $P < 0.05$ in the univariate analysis of PFS were included in the subsequent multivariate analysis. Two-sided $P < 0.05$ was considered statistically significant.

Table 1. Correlations between PLR and patient characteristics before targeted therapy.

Characteristic	Cases (n = 96)	PLR < 190 (n = 45)	PLR ≥ 190 (n = 51)	*P*
Age (years)				
<65	57 (59.4%)	28 (62.2%)	29 (56.9%)	0.59
≥65	39 (40.6%)	17 (37.8%)	22 (43.1%)	
Sex				
Male	40 (41.7%)	17 (37.8%)	23 (45.1%)	0.47
Female	56 (58.3%)	28 (62.2%)	28 (54.9%)	
ECOG PS				
<2	71 (73.9%)	32 (71.1%)	39 (76.5%)	0.55
≥2	25 (26.1%)	13 (28.9%)	12 (23.5%)	
Tumor location				
Left	41 (42.7%)	23 (51.1%)	18 (35.3%)	0.12
Right	55 (57.3%)	22 (48.9%)	33 (64.7%)	
Smoking				
Yes	21 (21.9%)	9 (20%)	12 (23.5%)	0.68
No	75 (78.1%)	36 (80%)	39 (76.5%)	
Metastases				
<3	53 (55.2%)	27 (60%)	26 (50.9%)	0.38
≥3	43(44.8%)	18 (40%)	25 (49.1%)	
Brain metastasis				
Yes	38 (39.6%)	21 (46.7%)	17 (33.3%)	0.18
No	58 (60.4%)	24 (53.3%)	34 (66.7%)	
Pleural effusion				
No	44 (45.8%)	24 (53.3%)	20 (39.2%)	0.17
Yes	52 (54.2%)	21 (46.7%)	31 (60.8%)	
BMI				
<25	75 (78.1%)	34 (75.6%)	41 (80%)	0.57
≥25	21 (21.9%)	11 (24.4%)	10 (20%)	
Albumin (g/L)				
<40	75 (78.1%)	33 (73.3%)	42 (82.4%)	0.29
≥40	21 (21.9%)	12 (26.7%)	9 (17.6%)	
EGFR mutation status				
Exon 19 del	44 (45.8%)	18 (40%)	26 (51%)	0.45
Exon 21 L858R	44 (45.8%)	22 (48.9%)	22 (43.1%)	
Other	8 (8.4%)	5 (11.1%)	3 (5.9%)	
Drugs				
Gefitinib	46 (47.9%)	22 (48.9%)	24 (47.1%)	0.98
Erlotinib	12 (12.5%)	5 (11.1%)	7 (13.7%)	
Icotinib	36 (37.5%)	17 (37.8%)	19 (37.3%)	
Afatinib	2 (2.1%)	1 (2.2%)	1 (1.9%)	

PLR, platelet/lymphocyte ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; EGFR, epidermal growth factor receptor; del, deletion.

Results

Patient characteristics

Ninety-six patients with cytological or histological confirmed NSCLC were enrolled in this study. As presented in Table 1, all clinical characteristics were comparable between the included patients after grouping by PLR. The median age at the time of diagnosis was 61 years (range, 27–83 years), and 58.3% of patients were women. Most patients had a Eastern Cooperative Oncology Group performance status of 0–2 (90.6%) and sensitive EGFR mutations (95.8%), including exon 19 deletion and exon 21 L858R. All patients received treatment with first-line EGFR-TKIs as follows: gefitinib (250 mg/day) in 46 patients, icotinib (375 mg/day) in 36 patients, erlotinib (150 mg/day) in 12 patients, and afatinib (40 mg/day) in 2 patients. There was no difference in the rates of use of each drug between the high and low PLR groups. The follow-up period ranged from 5.1 to 49.2 months (median, 21.7 months). No patients discontinued EGFR-TKI treatment because of severe adverse events. At the end of the last follow-up, 83 patients exhibited tumor progression.

The mean PLR and albumin level were 198 (range, 53–489) and 36.9 g/L (range, 25.1–45 g/L), respectively. According to the ROC curves, the optimal cutoff for PLR was 190, corresponding to maximum joint sensitivity and specificity. For PLR, the area under the ROC curve for PFS was 0.667, and the sensitivity and specificity were 64.7 and 64.4%, respectively (Figure 1). Based on the cutoff of 190, 51

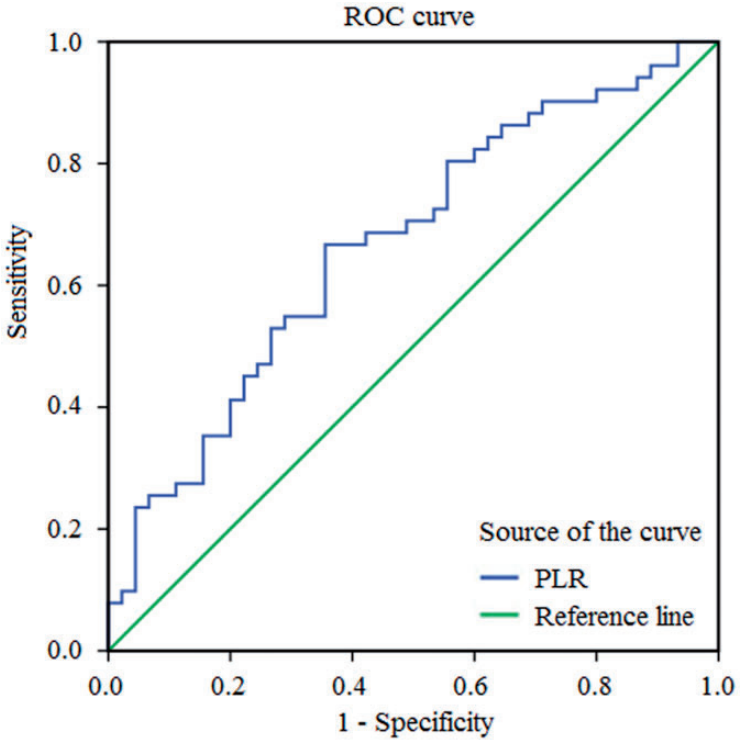

Figure 1. ROC curves for pretreatment PLR.
ROC, receiver operating characteristic; PLR, platelet/lymphocyte ratio.

patients (53.1%) had high pretreatment PLR (≥190). Patients were also divided into subgroups according to the lower limit level of serum albumin (<40 g/L versus ≥40 g/L). The relationships of clinicopathological parameters with pretreatment PLR in patients with EGFR-mutated NSCLC are presented in Table 1. There were no statistically significant differences between the two PLR groups.

Prognostic factors

The PLR < 190 group included 28 patients with PR, 13 patients with SD, and 4 patients with PD. Conversely, the PLR ≥190 group included 27, 14, and 10 patients with PR, SD, and PD, respectively. There was no significant difference of ORR (62.2% versus 52.9%) and DCR (91.1% versus 80.4%) between the two groups (Table 2). However, Kaplan–Meier analysis illustrated that patients in the PLR ≥190 group who received EGFR-TKIs had significantly shorter PFS than those in the PLR < 190 group ($P = 0.009$, Table 2). The 1-year PFS rate in the PLR ≥ 190 group was lower than that in the PLR < 190 group (55.6% versus 27.5%, $P = 0.008$, Table 2). Further analyses were performed to demonstrate whether PLR is an independent predictor for PFS in patients with NSCLC treated with EGFR-TKIs.

In univariate analysis, PLR ($P = 0.011$), pleural effusion ($P = 0.026$), and albumin levels ($P = 0.001$) were significantly associated with PFS (Table 3). In the multivariate Cox regression model, PLR (hazard ratio [HR] = 1.781, 95% CI = 1.123–2.825, $P = 0.014$) and albumin levels (HR = 0.388, 95% CI = 0.21–0.715, $P = 0.002$) were significantly associated with PFS, whereas pleural effusion was not predictive of PFS (Table 3). The Kaplan–Meier PFS curves for patients treated with EGFR-TKIs as stratified by PLR and albumin levels are presented in Figures 2 and 3.

PLR and toxicities

The primary toxicities possibly related to EGFR-targeted therapy are listed in Table 4. Adverse events were generally mild in both PLR groups. The most common grade 1/2 adverse events in both groups were non-hematologic toxicities, including rash, aminopherase elevation, anorexia, and fatigue. There were no significant differences in grade 1/2 adverse event rates between the groups (Table 4).

Table 2. Efficacy results of patients according to pretreatment PLR.

Variable	PLR < 190 (n = 45)	PLR ≥ 190 (n = 51)	*P*
Response			
PR, n (%)	28 (62.2%)	27 (52.9%)	
SD, n (%)	13 (28.9%)	14 (27.5%)	
PD, n (%)	4 (8.9%)	10 (19.6%)	
Response rate, %	62.2%	52.9%	0.36
95% CI	37.3–67.2	44.1–69.8	
Disease control rate, %	91.1%	80.4%	0.14
95% CI	70.3–93.3	79.5–96.4	
Median PFS (months)	12.4 months	6.6 months	0.009
95% CI	9.5–15.4	4.8–8.4	
One-year PFS rate (%)	55.6%	27.5%	0.008
95% CI	40.8–70.3	15.1–39.8	

PLR, platelet/lymphocyte ratio; PR, partial response, SD, stable disease; PD, progressive disease; CI, confidence interval; PFS, progression-free survival.

Table 3. Univariate and multivariate analyses of PFS in patients with advanced NSCLC.

Variable	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Age				
<65	1			
≥65	0.717 (0.458–1.122)	0.145		
Sex				
Male	1			
Female	1.153 (0.742–1.792)	0.526		
ECOG PS				
<2	1			
≥2	1.134 (0.68–1.893)	0.629		
Tumor location				
Left	1			
Right	1.5 (0.956–2.352)	0.078		
Smoking				
Yes	1			
No	1.18 (0.68–2.047)	0.555		
Metastases				
<3	1			
≥3	1.4 (0.898–2.183)	0.137		
Brain metastasis				
Yes	1			
No	0.741 (0.474–1.159)	0.189		
Pleural effusion				
No	1		1	
Yes	1.649 (1.061–2.562)	0.026	1.185 (0.748–1.879)	0.469
BMI				
<25	1			
≥25	1.117 (0.667–1.87)	0.675		
Albumin (g/L)				
<40	1		1	
≥40	0.376 (0.208–0.678)	0.001	0.388 (0.21–0.715)	0.002
PLR				
<190	1		1	
≥190	1.795 (1.147–2.811)	0.011	1.781 (1.123–2.825)	0.014
EGFR mutation status				
Exon 19 del	1			
Exon 21 L858R	1.047 (0.666–1.646)	0.842		

PFS, progression-free survival; NSCLC, non-small-cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; PLR, platelet/lymphocyte ratio; EGFR, epidermal growth factor receptor; del, deletion; HR, hazard ratio; CI, confidence interval.

Discussion

Targeted therapy is the recommended treatment for patients with EGFR-mutated advanced NSCLC. The efficacy and toxicities of targeted therapy are closely related to the EGFR mutation status. To date, no predictive factor for targeted therapy excluding the EGFR status has been extensively applied in the clinic. Previous studies investigated the utility of several biomarkers for predicting the prognosis of NSCLC, such as PLR, neutrophil counts, and CAR. However, the predictive roles

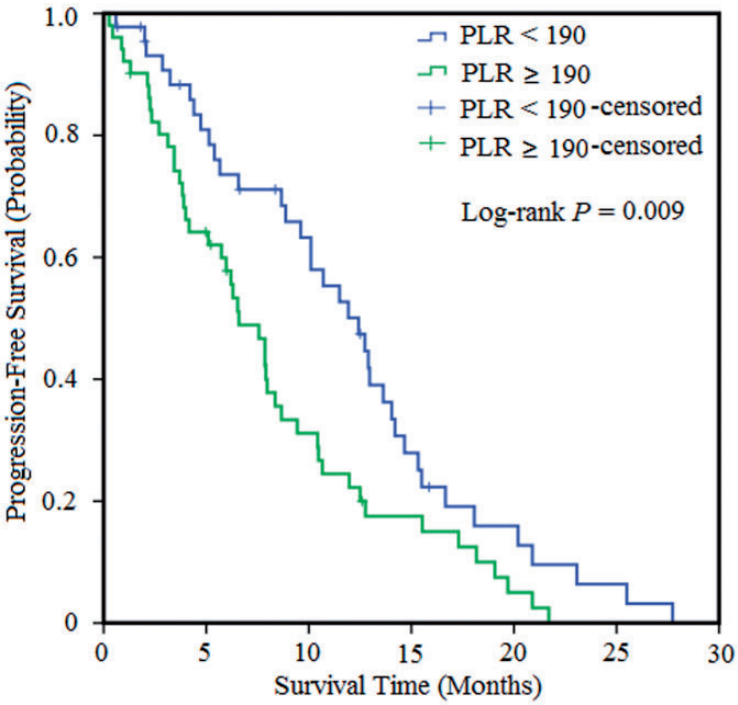

Figure 2. Kaplan–Meier curves for progression-free survival according to pretreatment PLR. PLR, platelet/lymphocyte ratio.

of these biomarkers are uncertain in the setting of precision medicine. Therefore, we conducted the present study to identify a helpful predictive factor for targeted treatment in patients with advanced NSCLC.

Chronic inflammation is involved in cancer formation and progression. PLR is a reproducible and inexpensive hematological marker that was suggested to be a marker of thrombotic and inflammatory conditions.[13,14] As previously reported, elevated pretreatment PLR in peripheral blood is an independent prognostic factors for various cancers, including advanced NSCLC.[15,16] One study revealed that high pretreatment PLR was associated with poor survival rates in patients with NSCLC. Nonetheless, the marker was not associated with the response to chemoradiotherapy.[17] Another study revealed that PLR was a prognostic marker in patients with metastatic NSCLC who received nivolumab independently of other prognostic factors.[18] To date, it remains unknown whether PLR is a prognostic factor for patients diagnosed with EGFR-mutated NSCLC.

In our study, we found that pretreatment PLR was significantly associated with PFS in patients with NSCLC who received EGFR-targeted therapy. Patients in the PLR $\geq$190 group had shorter PFS than those in the PLR $<$ 190 group ($P = 0.009$). Furthermore, the 1-year PFS rate in the PLR $\geq$190 group was inferior to that in the PLR $<$ 190 group ($P = 0.016$). Multivariate analysis indicated the possible role of PLR as a prognostic factor for patients with advanced NSCLC who received EGFR-targeted therapy. In this study, we found that hypoalbuminemia was negatively associated with the efficacy of EGFR therapy, which is in line with the

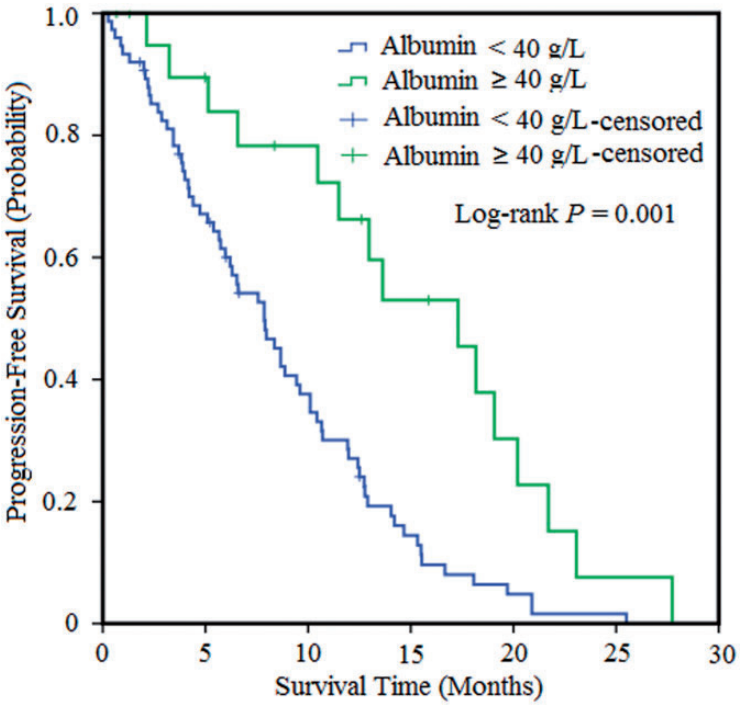

Figure 3. Kaplan–Meier curves for progression-free survival according to the albumin level.

Table 4. Treatment-related toxicities in patients according to PLR.

	Grade 1/2			Grade 3/4		
Toxicity	PLR < 190 (n = 45)	PLR ≥ 190 (n = 51)	*P*	PLR < 190 (n = 45)	PLR ≥ 190 (n = 51)	*P*
Rash	12	17	0.483	4	7	0.463
Pruritus	6	8	0.748	0	0	
Dizziness	3	8	0.17	0	0	
Fever	3	7	0.263	0	0	
Diarrhea	9	5	0.161	1	7	0.042
Fatigue	6	12	0.206	0	2	0.183
Nausea	7	10	0.608	0	0	
Vomiting	9	7	0.416	0	0	
Anorexia	10	19	0.112	0	0	
Aminopherase elevation	12	18	0.368	1	0	0.289
Dyspnea	6	6	0.819	1	4	0.22
Hemorrhage	1	5	0.128	0	1	0.35

PLR, platelet/lymphocyte ratio.

results of previous reports on several cancer types. Because the number of patients in this study was relatively small, further studies are needed to illuminate the relationship between PLR and survival in patients with EGFR-mutated NSCLC.

Our study revealed that PLR is a superior independent prognostic factor in patients with EGFR-mutated advanced lung cancer. In the recent decade, only the EGFR mutation status has been an effective predictive biomarker for efficacy and toxicity for targeted therapies such as gefitinib and erlotinib.[19,20] Recent studies did not consider the crucial impact of pretreatment PLR on therapeutic outcomes in patients receiving EGFR-TKIs compared with studies of chemotherapy and immunotherapy in advanced NSCLC. This study revealed that pretreatment PLR and albumin levels could be predictive of the efficacy of targeted therapy for NSCLC.

Nonetheless, this study had several limitations. First, this was a retrospective analysis with a relatively small number of patients with NSCLC. Hence, comprehensive multivariable analyses were not possible in the study. Second, the results were inevitably affected by residual confounding factors such as NLR, CAR, and hyperfibrinogenemia. Third, there may have been an elevated risk of patient selection bias in the study because this was a single-center investigation. Finally, four EGFR-targeted therapies were used, although previous studies proved that these drugs had similar efficacy.[21,22] However, the correlation of high pretreatment PLR with poor PFS was statistical significant and of vital importance clinically.

In conclusion, our study illustrated that pretreatment PLR may be an independent prognostic factor for patients with NSCLC receiving EGFR-TKI treatment. High pretreatment PLR may predict poor PFS for such patients. Further studies are needed to clarify the impact of pretreatment PLR on the outcome of EGFR-TKI treatment. Translational research is suggested to further investigate the mechanism of our clinical findings.

Acknowledgements

We would like to thank colleagues at Dongguan People's Hospital, Southern Medical University for their kind technical assistance, psychological support, theoretical guidance, and writing assistance during the present study. We would also like to thank the patients and their family members engaged in this clinical trial for their kindness in supporting our study. This manuscript has been released as a pre-print version in Research Square under the doi 10.21203/rs.2.12821/v1.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Dongguan Social Science and Technology Development Project (grant no. 201750715001285).

ORCID iD

Kejun Liu https://orcid.org/0000-0003-1721-2723

References

1. Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30.
2. Liu KJ and Wu HY. A retrospective analysis of cisplatin, pemetrexed, and bevacizumab in previously treated non-small-cell lung cancer. *Oncotarget* 2015; 6: 22750–22757.
3. Chen F, Cole P and Bina WF. Time trend and geographic patterns of lung adenocarcinoma in the united states, 1973–2002. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 2724–2729.

4. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012; 13: 239–246.
5. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* 2005; 97: 339–346.
6. Gomes M, Teixeira AL, Coelho A, et al. The role of inflammation in lung cancer. *Adv Exp Med Biol* 2014; 816: 1–23.
7. Shiels MS, Pfeiffer RM, Hildesheim A, et al. Circulating inflammation markers and prospective risk for lung cancer. *J Natl Cancer Inst* 2013; 105: 1871–1880.
8. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. *Nature* 2008; 454: 436–444.
9. Zhang WW, Liu KJ, Hu GL, et al. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to othersystemic inflammatory response markers in ovarian cancer patients. *Tumour Biol* 2015; 36: 8831–8837.
10. Zhang WW, Liu KJ, Ye B, et al. Pretreatment C-reactive protein/albumin ratio is associated with poor survival in patients with stage IB-IIA cervical cancer. *Cancer Med* 2018; 7: 105–113.
11. Gonzalez Barcala FJ and Garcia Prim JM. Platelet count: association with prognosis in lung cancer. *Med Oncol* 2010; 27: 357–362.
12. Aoe K, Hiraki A and Ueoka H. Thrombocytosis as a useful prognostic indicator in patients with lung cancer. *Respiration* 2004; 71: 170–173.
13. Smith RA, Ghaneh P, Sutton R, et al. Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. *J Gastrointest Surg* 2008; 12: 1422–1428.
14. Wang D, Yang JX, Cao DY, et al. Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. *Onco Targets Ther* 2013; 6: 211–216.
15. Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol* 2013; 88: 218–230.
16. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2014; 23: 1204–1212.
17. Unal D, Eroglu C, Kurtul N, et al. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis? *Asian Pac J Cancer Prev* 2013; 14: 5237–5242.
18. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer* 2017; 111: 176–181.
19. Perez-Soler R, Chachoua A, Hammond LA, et al. Determinants of tumor response and survival with erlotinib in patients with non–small-cell lung cancer. *J Clin Oncol* 2004; 22: 3238–3247.
20. Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003; 290: 2149–2158.
21. Burotto M, Manasanch EE, Wilkerson J, et al. Gefitinib and erlotinib in metastatic non-small cell lung cancer: a meta-analysis of toxicity and efficacy of randomized clinical trials. *Oncologist* 2015; 20: 400–410.
22. Shi YK, Zhang L, Liu XQ, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. *Lancet Oncol* 2013; 14: 953–961.