

The combination of fibrinogen concentrations and the platelet-to-lymphocyte ratio predicts survival in patients with advanced lung adenocarcinoma treated with EGFR-TKIs

Journal of International Medical Research

49(4) 1–11

© The Author(s) 2021

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/03000605211004021

journals.sagepub.com/home/imr



Qiong He^{1,2}, Yamin Li¹, Xihong Zhou¹,
Wen Zhou¹, Chunfang Xia^{1,2}, Ruzhe Zhang^{1,2},
Zhengjie Zhang^{1,2}, Aiyang Hu^{1,2}, Siyin Peng^{1,2}
and Jing Li^{1,2} 

Abstract

Objective: This study aimed to identify a predictive marker of response to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in patients with EGFR-mutant advanced lung adenocarcinoma.

Methods: A cohort of 190 patients with EGFR-mutant advanced lung adenocarcinoma was analyzed. Receiver operating characteristic curve analysis was used to evaluate the optimal cutoffs for fibrinogen levels, the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR) for predicting progression-free survival (PFS). Univariate and multivariate survival analyses were performed to identify factors correlated with PFS and overall survival (OS).

Results: High NLR was associated with worse performance status. In univariate analysis, fibrinogen levels, NLR, and PLR were correlated with OS and PFS. In multivariate analysis, all three variables remained predictive of OS, whereas only fibrinogen levels and PLR were independent prognostic factors for PFS. Furthermore, the combination of fibrinogen levels and PLR (F-PLR

¹Clinical Nursing Teaching and Research Section, The Second Xiangya Hospital, Central South University, Changsha, Hunan Province, China

²Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, Hunan Province, China

Corresponding author:

Jing Li, Clinical Nursing Teaching and Research Section, The Second Xiangya Hospital, Central South University, No. 139 Renmin Road, Changsha, Hunan 410011, China. Email: lijing1118@csu.edu.cn



score) could stratify patients into three groups with significantly different prognoses, and the score was independently predictive of survival.

Conclusion: The F-PLR score predicted the prognosis of patients with EGFR-mutant advanced lung adenocarcinoma who received EGFR-TKIs, and this score may serve as a convenient blood-based marker for identifying high-risk patients.

Keywords

Lung adenocarcinoma, epidermal growth factor receptor, tyrosine kinase inhibitor, fibrinogen, platelet-to-lymphocyte ratio, prognosis, neutrophil-to-lymphocyte ratio, overall survival, progression-free survival

Date received: 27 February 2021; accepted: 2 March 2021

Introduction

Lung cancer is the leading cause of death globally, and non-small cell lung cancer (NSCLC) is the most common form of lung cancer.¹ Approximately 70% of patients are diagnosed with advanced or locally advanced disease, and their prognosis is poor. For patients harboring epidermal growth factor receptor (EGFR) mutations, EGFR tyrosine kinase inhibitors (TKIs) have proven superior to chemotherapy in patients with relapsed or advanced lung cancer in clinical trials.²⁻⁶ For first-generation EGFR-TKIs (including gefitinib, erlotinib, and icotinib), the median progression-free survival (PFS) was approximately 8 to 10 months, and nearly all patients inevitably experience drug resistance and treatment failure. However, the response to treatment varies significantly among individuals, and a useful marker for predicting prognosis is lacking.

Local and systemic inflammation is a hallmark of cancer.⁷ Recently accumulated evidence indicates that inflammation is an important factor affecting patients' responses to treatment and prognosis. A series of blood-based markers, including

the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been reported to be effective for predicting patients' survival in various cancers,⁸⁻¹⁰ including NSCLC.¹¹ Blood coagulation disorder is a common complication of malignant tumors, and recent studies demonstrated that coagulation system activation is associated with progression and metastasis in various cancers.^{12,13} Therefore, fibrinogen, an importation protein mediating coagulation pathways, is considered a prognostic factor for patients with cancer. Several studies evaluated the prognostic role of fibrinogen in various cancers.¹⁴⁻¹⁶ In NSCLC, Zhong et al.¹⁷ reported in a meta-analysis that the plasma fibrinogen level is an independent predictor for overall survival (OS). Recently, an increasing number of studies have evaluated the prognostic role of the combination of fibrinogen levels and other blood-based markers, such as NLR and PLR, in patients with NSCLC¹⁸ and breast cancer.¹⁹ However, the prognostic significance of combinations of these variables in patients with advanced NSCLC has yet to be evaluated.

In the present study, we retrospectively analyzed a cohort of 194 patients with

advanced EGFR-mutant lung adenocarcinoma to evaluate the prognostic role of NLR, PLR, fibrinogen, and their combination following EGFR-TKI treatment.

Patients and methods

Patient selection

Patients who were pathologically diagnosed with lung adenocarcinoma at Second Xiangya Hospital (Changsha, China) between January 2016 and December 2018 were consecutively and retrospectively recruited. All patients underwent genetic testing via next-generation sequencing or the amplification-refractory mutation system, and the presence of mutant EGFR was confirmed. All patients in the present cohort consented to treatment with a first-generation EGFR-TKI (gefitinib, erlotinib, or icotinib) as the first-line treatment, and a blood test was performed within 1 week prior to treatment. Patients with histories of other malignant tumors, chronic inflammatory diseases, recent steroid therapy, acute infection, or inflammation were excluded. All patient personal information was de-identified. Approval was obtained from the Ethical Committee and institutional review board of Second Xiangya Hospital, Central South University (Changsha, Hunan, China) on May 5, 2020. The requirement for informed consent was waived by the consent was waived by the Ethical Committee of the institution because of the retrospective nature of the research.

Data collection and follow-up

The patients' clinicopathological characteristics (including age, sex, smoking history, brain metastasis status, Eastern Cooperative Oncology Group performance status [ECOG PS], EGFR mutation status, blood routine test data, and coagulation

function test results) were obtained from the electronic medical record system of Second Xiangya Hospital. NLR was calculated as follows: $NLR = \text{neutrophil count} / \text{lymphocyte count}$. PLR was calculated as follows: $PLR = \text{platelet count} / \text{lymphocyte count}$. ECOG PS was used to evaluate the patients' physical status (on a scale of 0–5, with higher scores indicating a worse general condition). PFS was calculated from the date of diagnosis to that of disease progression (based on Response Evaluation Criteria in Solid Tumors 1.1) or death. OS was calculated from the date of diagnosis to that of death of any cause or the last follow-up date (April 1, 2020). The reporting of this study conforms to the STROBE statement.²⁰

F-PLR score

The F-PLR score was created by combining fibrinogen levels and PLR. For both fibrinogen levels and PLR, patients were given a score of 1 if the value exceeded the cutoff, whereas a score of 0 was given for lower values. Thus, the total F-PLR ranged 0 to 2.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 (IBM, Armonk, NY, USA). Receiver operating characteristic (ROC) curves were used to calculate the optimal cutoffs for fibrinogen levels, NLR, and PLR. Survival analysis was performed using the Kaplan–Meier method. The chi-squared and log-rank tests were used to compare the baseline clinical characteristics and survival curves, respectively. The predictive factors for survival were evaluated via univariate and multivariate analyses using the Cox hazards regression method. All tests were two-sided, and $P < 0.05$ indicated statistical significance.

Results

Patient characteristics

In total, 190 patients with advanced EGFR-mutant lung adenocarcinoma were enrolled in the present study. The clinicopathological characteristics of the cohort are presented in Table 1. The mean age of all patients was 60 years (range, 28–79 years), and 104 (54.7%) patients were female. Most patients (133, 70.0%) were non-smokers. In total, 155 (80.4%) patients had an ECOG PS of 0 or 1. Twenty-four patients had brain metastasis, and five patients received whole-brain radiation therapy concurrent with TKI therapy. Among all patients, 80 (42.1%) patients carried the L858R mutation in exon 21, 103 (54.2%) displayed exon 19 deletion, and 7 (3.7%) had other rare mutations. According to the ROC curve, the area under the ROC curves for fibrinogen levels, NLR and PLR were 0.644, 0.517, and 0.522, respectively. The optimal cutoffs for fibrinogen levels, NLR, and PLR were 3.75 g/L, 3.28, and 273.84, respectively. Hence, 73 (38.4%) patients were assigned to the high fibrinogen group, 92 (48.4%) patients were assigned to the high NLR group, and 33 (17.4%) patients were assigned to the high PLR group.

Relationships of fibrinogen levels, NLR, and PLR with clinicopathological characteristics

The relationships of fibrinogen levels, NLR, and PLR with patients' clinical characteristics are presented in Table 2. Patients with high NLR had worse ECOG PS ($P=0.003$). Fibrinogen levels, NLR, and PLR did not display significant correlations with age, smoking status, brain metastasis, and the EGFR mutation status based on the aforementioned cutoffs.

Table 1. Baseline characteristics of the patients.

Characteristics	N (%)
Age	
Median	60
Range	28–79
Sex	
Male	86 (45.3)
Female	104 (54.7)
Smoking status	
Non-smoker	133 (70.0)
Current or ex-smoker	57 (30.0)
ECOG PS	
0–1	155 (80.4)
2	35 (19.6)
Brain metastasis	
Yes	24 (12.6)
No	166 (87.4)
EGFR mutation	
L858R	80 (42.1)
Exon 19 deletion	103 (54.2)
Other	7 (3.7)
NLR	
Low	98 (51.6)
High	92 (48.4)
PLR	
Low	157 (82.6)
High	33 (17.4)
Fibrinogen	
Low	117 (61.6)
High	73 (38.4)

ECOG PS, Eastern Cooperative Oncology group performance status; EGFR, epidermal growth factor receptor; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Univariate and multivariate Cox regression analyses of PFS and OS

In univariate analysis, ECOG PS, fibrinogen levels, NLR, and PLR were significantly associated with PFS ($P=0.013$, $P<0.001$, $P=0.013$, and $P<0.001$, respectively, Figure 1a–c) and OS ($P<0.001$, $P=0.025$, $P=0.005$, and $P=0.001$, respectively, Figure 1d–f), whereas other clinical characteristics, including age, gender, smoking status, brain metastasis, and mutation type, were not significantly associated

Table 2. Clinicopathological characteristics of the patients according to fibrinogen levels, NLR, and PLR.

Characteristics	Low fibrinogen	High fibrinogen	P	Low NLR	High NLR	P	Low PLR	High PLR	P
Age									
<60	66 (34.7%)	37 (19.5%)	0.458	56 (29.5%)	47 (24.7%)	0.467	81 (42.6%)	22 (11.6%)	0.128
≥60	51 (26.8%)	36 (18.9%)		42 (22.1%)	45 (23.7%)		76 (40.0%)	11 (5.8%)	
Sex									
Female	66 (34.7%)	38 (20.0%)	0.653	60 (31.6%)	44 (23.2%)	0.080	86 (45.3%)	18 (9.5%)	1.000
Male	51 (26.8%)	35 (18.4%)		38 (10.0%)	48 (25.3%)		71 (37.4%)	15 (7.9%)	
Smoking status									
No	83 (43.7%)	50 (26.3%)	0.747	69 (36.3%)	64 (33.7%)	1.000	108 (56.8%)	25 (13.2%)	0.533
Yes	34 (17.9%)	23 (12.1%)		29 (15.3%)	28 (14.7%)		49 (25.8%)	8 (4.2%)	
ECOG PS									
0-1	98 (51.6%)	57 (30.0%)	0.342	88 (46.3%)	67 (35.3%)	0.003	132 (69.5%)	23 (12.1%)	0.080
2	19 (10.0%)	16 (8.4%)		10 (5.3%)	25 (13.1%)		25 (13.2%)	10 (5.2%)	
Brain metastasis									
Yes	11 (5.8%)	13 (6.8%)	0.116	13 (6.8%)	11 (5.8%)	0.830	19 (10.0%)	5 (2.6%)	0.575
No	106 (55.8%)	60 (31.6%)		85 (44.7%)	81 (42.6%)		138 (72.6%)	28 (14.7%)	
EGFR mutation									
L858R	47 (24.7%)	33 (17.4%)	0.366	41 (21.6%)	39 (20.5%)	0.179	69 (36.3%)	11 (5.8%)	0.188
Exon 19 deletion	64 (33.7%)	39 (20.5%)		51 (26.8%)	52 (27.4%)		81 (42.6%)	22 (11.6%)	
Other	6 (3.2%)	1 (0.5%)		6 (3.2%)	1 (0.5%)		7 (3.7%)	0 (0%)	

ECOG PS, Eastern Cooperative Oncology group performance status; EGFR, epidermal growth factor receptor; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

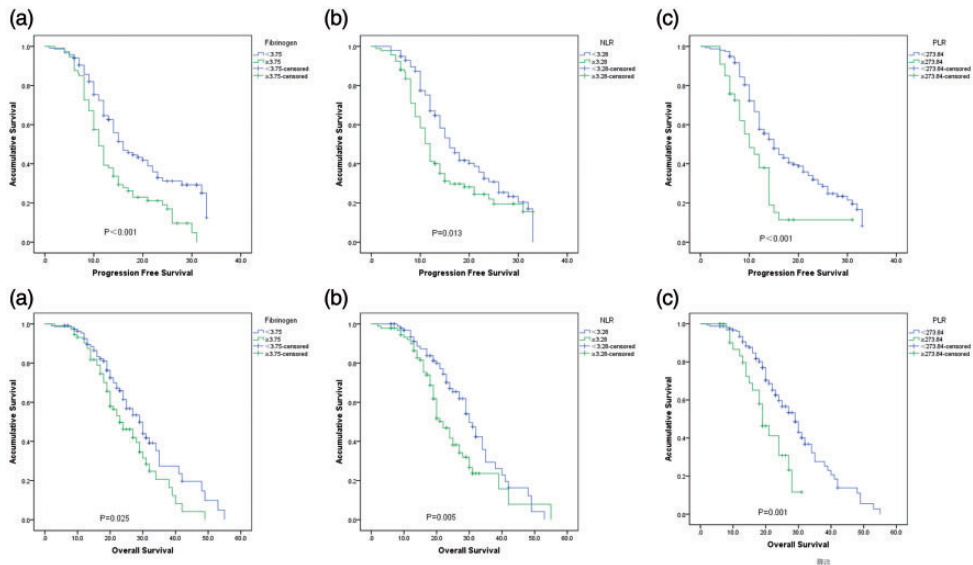


Figure 1. Kaplan–Meier survival curves for progression-free survival according to fibrinogen levels (a), NLR (b), and PLR (c) and for overall survival according to fibrinogen levels (d), NLR (e), and PLR (f) in patients with epidermal growth factor receptor-mutant lung adenocarcinoma treated with first-generation epidermal growth factor receptor tyrosine kinase inhibitors. NLR, neutrophil-to-lymphocyte ratio, PLR, platelet-to-lymphocyte ratio.

with patient survival in the present analysis (Table 3).

In the multivariate Cox regression analysis, PLR (hazard ratio [HR]=1.843; 95% confidence interval [CI]=1.149–2.957; $P=0.011$) and fibrinogen levels (HR = 1.890; 95% CI = 1.323–2.699; $P < 0.001$) were independent prognostic factors for PFS. Meanwhile, PLR (HR = 1.729; 95% CI = 1.018–2.936; $P=0.0043$), NLR (HR = 1.552; 95% CI = 1.012–2.381; $P=0.0044$), and fibrinogen levels (HR = 1.565; 95% CI = 1.047–2.340; $P=0.029$) were identified as independent predictors of OS (Table 4).

Prognostic value of the F–PLR score

In total, 100 (52.6%) patients had an F–PLR score of 0, 75 (39.5%) patients had an F–PLR score of 1, and 15 (7.9%) patients had an F–PLR score of 2.

The median PFS times for patients with F–PLR scores of 0, 1, and 2 were 18.3, 12.2, and 7.8 months, respectively ($P < 0.001$; Figure 2a), and the median OS times for these patients were 30.1, 23.4, and 18.8 months, respectively ($P=0.021$; Figure 2b).

Discussion

In the present study, we retrospectively analyzed a cohort of patients with EGFR-mutant lung adenocarcinoma who received EGFR-TKIs to evaluate the prognostic value of the blood-based biomarkers fibrinogen, NLR, and PLR. We found that PLR, NLR, and plasma fibrinogen levels were correlated with PFS and OS. Multivariate analysis demonstrated that high PLR and high plasma fibrinogen levels were independent prognostic factors for worse PFS, and high NLR, PLR, and fibrinogen levels were

Table 3. Univariate analysis of potential factors associated with PFS and OS.

Variables	PFS			OS		
	N	MST (m)	P	N	MST (m)	P
Age						
<60	103	14.3	0.625	103	26.8	0.612
≥60	87	14.0		87	29.5	
Sex						
Female	104	14.4	0.558	104	28.9	0.275
Male	86	12.3		86	23.7	
Smoking status						
No	133	14.2	0.291	133	29.2	0.228
Yes	57	12.2		57	24.1	
ECOG PS						
0–1	155	14.6	0.013	155	29.2	<0.001
2	35	11.2		35	19.0	
Brain metastasis						
Yes	24	11.4	0.467	24	27.3	0.822
No	166	13.9		166	24.1	
EGFR mutation						
L858R	80	11.6	0.314	80	21.7	0.135
Exon 19 deletion	103	15.3		103	26.8	
Other	7	11.7		7	NR	
Fibrinogen						
Low	117	16.4	<0.001	117	28.8	0.025
High	73	11.2		73	23.2	
NLR						
Low	98	16.1	0.013	98	30.6	0.005
High	92	12.1		92	22.1	
PLR						
Low	157	15.2	<0.001	157	28.6	0.001
High	33	9.8		33	18.9	

PFS, progression-free survival; OS, overall survival, ECOG PS, Eastern Cooperative Oncology group performance status; EGFR, epidermal growth factor receptor; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MST, median survival time.

independent prognostic factors for worse OS. Moreover, the combination of fibrinogen levels and PLR could better predict the survival of patients, thus revealing a novel marker for patient stratification.

Lung adenocarcinoma can be divided into two groups according to the gene mutation status. For patients without known driver gene mutations (e.g., EGFR, ALK, ROS-1), chemotherapy and/or radiation therapy is the major treatment

modality. For patients with driver gene mutations, targeted therapy is the major treatment modality. Although several trials demonstrated that EGFR-TKIs improve PFS in patients with advanced NSCLC harboring EGFR mutations, drug resistance is nearly inevitable, representing a major challenge for clinicians. Thus, biomarkers to predict drug effectiveness and facilitate patient stratification and treatment adjustment are urgently needed.

Table 4. Multivariable Cox regression analyses of PFS and OS

Variables	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
NLR				
High	1.285 (0.876–1.886)	0.200	1.552 (1.012–2.381)	0.044
Low				
PLR				
High	1.843 (1.149–2.957)	0.011	1.729 (1.018–2.936)	0.043
Low				
Fibrinogen				
High	1.890 (1.323–2.699)	<0.001	1.565 (1.047–2.340)	0.029
Low				

PFS, progression-free survival; OS, overall survival, NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

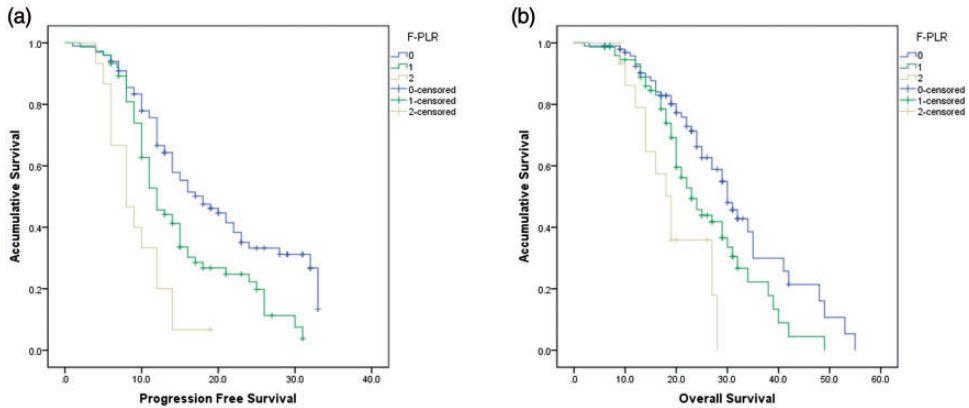


Figure 2. Kaplan–Meier curves of progression-free survival (a) and overall survival (b) according to the F-PLR score (0 = low fibrinogen and low PLR, 1 = low fibrinogen and high PLR or high fibrinogen and low PLR, 2 = high fibrinogen and high PLR). PLR, platelet-to-lymphocyte ratio.

Biomarkers predictive of EGFR-TKI effectiveness are lacking. It has been reported that PD-L1 expression and the immune microenvironment are associated with EGFR-TKI effectiveness,²¹ indicating that the inflammatory status is associated with drug response. Inflammatory responses represent a common complication of malignant tumors because cytokines released by tumor cells can induce systemic inflammation.²² Systemic inflammation affects the counts of inflammation-related cells,

including neutrophils, lymphocytes, and platelets. Thus, blood-based biomarkers that can be used to characterize the inflammatory status have proven effective for predicting patient prognosis for various cancers. NLR and PLR are the most widely studied biomarkers, and they have proven prognostic significance in various cancers.^{8,23,24} Regarding NSCLC, studies reported that NLR and PLR could predict patient survival in both early and advanced stages.^{25–28} In the present study, we

identified PLR and NLR as independent prognostic factors for PFS, in line with previous reports. These results further indicated that systemic inflammation is involved in the development of EGFR-TKI resistance; however, the underlying mechanism requires further investigation. Targeting systemic inflammation might represent a promising strategy to delay drug resistance. Concerning OS, NLR and PLR were also predictive factors. This may be attributable to the impact of follow-up treatment. Generally, the follow-up treatment after EGFR-TKI resistance includes targeted therapy and chemotherapy, which have different mechanisms of resistance, thereby limiting the ability of a single biomarker to predict OS.

Fibrinogen is a protein synthesized by the liver that mediates blood coagulation, and it is an acute reactive protein involved in the inflammatory process. Recent evidence indicated the involvement of fibrinogen in a series of cancer-related processes, including cell proliferation, angiogenesis, and epithelial–mesenchymal transformation, which are correlated with cancer progression and drug resistance.²⁹ Clinical studies have evaluated the prognostic role of fibrinogen in various cancers.^{9,14,30} Regarding lung cancer, Zhong et al.¹⁷ conducted a meta-analysis of 16 studies involving 6881 patients, finding that a plasma fibrinogen concentration of ≥ 4 g/L portended worse OS. In the present study, we also found that a higher fibrinogen level is an independent prognostic factor for PFS and OS, as reported previously.

Because multiple blood-based prognostic biomarkers have been discovered in various cancers, the combination of biomarkers to increase prognostic significance and improve patient stratification is increasingly emphasized. Several studies evaluated the combination of fibrinogen levels with other inflammatory markers, including NLR, PLR, and the lymphocyte-

to-monocyte ratio, in gastric cancer,³¹ colorectal adenocarcinoma,³² and esophageal carcinoma.³³ The findings highlighted the promise of such combinations for predicting patient survival. Liang et al.¹⁸ retrospectively analyzed a cohort of patients with NSCLC and found that the combination of fibrinogen levels and NLR (F–NLR) has potential as a novel and useful blood marker for predicting postoperative survival. In the present study, we found that fibrinogen levels and PLR were independent prognostic factors for PFS and OS, and the F-PLR score could stratify patients with NSCLC into three distinctive risk groups, thereby improving the prognostic significance over either biomarker alone.

The present study had obvious limitations. First, because of the retrospective nature of the study, patient selection bias and follow-up bias were inevitable. Second, because of the limited sample size, only 15 patients had an F-PLR score of 2. Although significant differences were noted among the groups, the results should be interpreted with caution. Further prospective studies are required to validate the role of fibrinogen and other blood-based biomarkers in predicting prognosis in patients with EGFR-mutant NSCLC receiving first-line EGFR-TKI treatment.

In summary, our research demonstrated that plasma fibrinogen levels, NLR, and PLR are promising and easily measured biomarkers that could be used to predict the prognosis of patients with advanced lung adenocarcinoma who received EGFR-TKIs. In addition, the combination of fibrinogen levels and PLR may represent a promising biomarker with higher predictive potential that is worthy of further investigation.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Jing Li  <https://orcid.org/0000-0001-5755-4950>

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; 361: 947–957.
3. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12: 735–742.
4. Shi YK, Wang L, Han BH, et al. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. *Ann Oncol* 2017; 28: 2443–2450.
5. Schuler M, Paz-Ares L, Sequist LV, et al. First-line afatinib for advanced EGFRm+ NSCLC: Analysis of long-term responders in the LUX-Lung 3, 6, and 7 trials. *Lung Cancer* 2019; 133: 10–19.
6. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N Engl J Med* 2020; 382: 41–50.
7. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144: 646–674.
8. Cai G, Yu J and Meng X. Predicting Prognosis and Adverse Events by Hematologic Markers in Patients with Locally Advanced Esophageal Squamous Cell Carcinoma Treated with Neoadjuvant Chemoradiotherapy. *Cancer Manag Res* 2020; 12: 8497–8507.
9. Gu L, Wang M, Cui X, et al. Clinical significance of peripheral blood-derived inflammation markers in advanced gastric cancer after radical resection. *BMC Surg* 2020; 20: 219.
10. Drpa G, Sutic M, Baranasic J, et al. Neutrophil-to-lymphocyte ratio can predict outcome in extensive-stage small cell lung cancer. *Radiol Oncol* 2020; 54: 437–446.
11. Matsubara T, Takamori S, Haratake N, et al. The impact of immune-inflammation-nutritional parameters on the prognosis of non-small cell lung cancer patients treated with atezolizumab. *J Thorac Dis* 2020; 12: 1520–1528.
12. Tsimafeyev IV, Demidov LV, Madzhuga AV, et al. Hypercoagulability as a prognostic factor for survival in patients with metastatic renal cell carcinoma. *J Exp Clin Cancer Res* 2009; 28: 30.
13. Kvolik S, Jukic M, Matijevic M, et al. An overview of coagulation disorders in cancer patients. *Surg Oncol* 2010; 19: e33–e46.
14. Yang S, Guan H, Wang S, et al. Plasma Fibrinogen Predicts the Prognosis of Bladder Cancer Patients After Radical Cystectomy. *Cancer Manag Res* 2020; 12: 9303–9314.
15. Li Y, Li Z, Deng K, et al. Fibrinogen/Lymphocyte Count Ratio Can Be Used as a New Indicator of Prognosis in Patients with Hepatocellular Carcinoma After Radical Resection. *Cancer Manag Res* 2020; 12: 9057–9066.
16. Chung KH, Lee JC, Lee J, et al. Serum fibrinogen as a diagnostic and prognostic biomarker for pancreatic ductal adenocarcinoma. *Pancreatol* 2020; 20: 1465–1471.
17. Zhong H, Qian Y, Fang S, et al. Prognostic Value of Plasma Fibrinogen in Lung Cancer Patients: A Meta-Analysis. *J Cancer* 2018; 9: 3904–3911.
18. Liang HG, Gao K, Jia R, et al. Prognostic significance of the combination of preoperative fibrinogen and the neutrophil-lymphocyte ratio in patients with non-small

- cell lung cancer following surgical resection. *Oncol Lett* 2019; 17: 1435–1444.
19. Cao X, Zhou Y, Mao F, et al. Combination of preoperative fibrinogen concentration and neutrophil-to-lymphocyte ratio for prediction of the prognosis of patients with resectable breast cancer. *Oncol Lett* 2020; 20: 200.
 20. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
 21. Yang CY, Liao WY, Ho CC, et al. Association between programmed death-ligand 1 expression, immune microenvironments, and clinical outcomes in epidermal growth factor receptor mutant lung adenocarcinoma patients treated with tyrosine kinase inhibitors. *Eur J Cancer* 2020; 124: 110–122.
 22. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014; 15: e493–e503.
 23. Allen J, Cernik C, Bajwa S, et al. Association of Neutrophil, Platelet, and Lymphocyte Ratios with the Prognosis in Unresectable and Metastatic Pancreatic Cancer. *J Clin Med* 2020; 9: 3283.
 24. Casadei Gardini A, Scarpi E, Valgiusti M, et al. Prognostic role of a new index (multi-inflammatory index) in patients with metastatic colorectal cancer: results from the randomized ITACa trial. *Ther Adv Med Oncol* 2020; 12: 1758835920958363.
 25. Li A, Mu X, He K, et al. Prognostic value of lymphocyte-to-monocyte ratio and systemic immune-inflammation index in non-small-cell lung cancer patients with brain metastases. *Future Oncol* 2020; 16: 2433–2444.
 26. Zhang N, Jiang J, Tang S et al. Predictive value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in non-small cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. *Int Immunopharmacol* 2020; 85: 106677.
 27. Deng C, Zhang N, Wang Y, et al. High systemic immune-inflammation index predicts poor prognosis in advanced lung adenocarcinoma patients treated with EGFR-TKIs. *Medicine (Baltimore)* 2019; 98: e16875.
 28. Guo W, Cai S, Zhang F, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected non-small cell lung cancer. *Thorac Cancer* 2019; 10: 761–768.
 29. Zhang X, Wang F, Huang Y, et al. FGG promotes migration and invasion in hepatocellular carcinoma cells through activating epithelial to mesenchymal transition. *Cancer Manag Res* 2019; 11: 1653–1665.
 30. Guo Y, Liu J, Zhang W, et al. Prognostic Value of Fibrinogen and Lymphocyte Count in Intermediate and High Risk Gastrointestinal Stromal Tumors. *Cancer Manag Res* 2020; 12: 8149–8157.
 31. Yamamoto M, Kurokawa Y, Kobayashi N, et al. Prognostic Value of the Combined Index of Plasma Fibrinogen and the Neutrophil-Lymphocyte Ratio in Gastric Cancer. *World J Surg* 2020; 44: 207–212.
 32. Li X, An B, Zhao Q, et al. Combined fibrinogen and neutrophil-lymphocyte ratio as a predictive factor in resectable colorectal adenocarcinoma. *Cancer Manag Res* 2018; 10: 6285–6294.
 33. Kijima T, Arigami T, Uchikado Y, et al. Combined fibrinogen and neutrophil-lymphocyte ratio as a prognostic marker of advanced esophageal squamous cell carcinoma. *Cancer Sci* 2017; 108: 193–199.