


# High fibrinogen-albumin ratio index predicts poor prognosis for lung adenocarcinoma patients undergoing epidermal growth factor receptor-tyrosine kinase inhibitor treatments

Xiayan Zhao, MD, Na Zhang, MD, Haixia Zhang, MD, Ping Liu, MD, PhD, Jinan Ma, MD, PhD, Chunhong Hu, MD, PhD, Xianling Liu, MD, PhD, Tao Hou, MD\* 

## Abstract

Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKIs) have become the preferred therapy as first-line treatment of non-small cell lung cancer patients harboring sensitizing EGFR mutations. However, the prognostic indicators are limited. The present study aimed to assess the prognostic value of immune-inflammation factors, fibrinogen-albumin ratio index (FARI), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) in EGFR-Mutant lung adenocarcinoma patients receiving first-generation EGFR-TKIs treatment.

194 patients were included in this retrospective analysis. FARI was calculated as fibrinogen / albumin. Receiver operating characteristic curve was used to evaluate the optimal cut-off value for FARI, NLR, and PLR to progression free survival (PFS). Univariate and multivariate survival analysis were performed to identify factors correlated with PFS and overall survival (OS).

Applying cut-offs of  $\geq 0.08$  (FARI),  $\geq 3.28$  (NLR), and  $\geq 273.85$  (PLR), higher FARI or NLR was associated with worse Eastern Cooperative Oncology Group performance status (ECOG PS) ( $P = .018$ ,  $.002$ , respectively), and there were more males in high NLR group ( $P = .043$ ). In univariate analysis, ECOG PS status, NLR, PLR, and FARI were significantly associated with PFS ( $P = .017$ ,  $.004$ ,  $< .001$ ,  $.001$ , respectively) as well as OS ( $P < .001$ ,  $= .001$ ,  $.002$ ,  $.023$ , respectively). In multivariate analysis, PLR (hazard ratios [HR] 1.692; 95% CI 1.054–2.715;  $P = .029$ ) and FARI (HR 1.496; 95% CI 1.031–2.172;  $P = .034$ ) were independent prognostic factors for PFS. While only ECOG PS status (HR 2.052; 95% CI 1.272–3.310;  $P = .003$ ) was independently correlated with OS.

FARI is independently associated with PFS in EGFR-Mutant lung adenocarcinoma patients receiving first-line EGFR-TKIs treatment.

**Abbreviations:** 95%CI = confidence intervals, ECOG PS = Eastern Cooperative Oncology Group performance status, EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor, FARI = fibrinogen-albumin ratio index, HR = hazard ratios, NLR = neutrophil to lymphocyte ratio, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression free survival, PLR = platelet to lymphocyte ratio, ROC = receiver operating characteristic.

**Keywords:** epidermal growth factor receptor-tyrosine kinase inhibitor, non-small cell lung cancer, prognosis, fibrinogen-albumin ratio index

Editor: Jianxun Ding.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Department of Oncology, the Second Xiangya Hospital, Central South University, Changsha, Hunan, China.

\* Correspondence: Tao Hou, Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China (e-mail: houtao@csu.edu.cn).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Zhao X, Zhang N, Zhang H, Liu P, Ma J, Hu C, Liu X, Hou T. High fibrinogen-albumin ratio index predicts poor prognosis for lung adenocarcinoma patients undergoing epidermal growth factor receptor-tyrosine kinase inhibitor treatments. *Medicine* 2020;99:46(e23150).

Received: 20 May 2020 / Received in final form: 25 August 2020 / Accepted: 15 October 2020

<http://dx.doi.org/10.1097/MD.00000000000023150>

## 1. Introduction

Lung cancer is the leading cause of cancer death among both in China and worldwide,<sup>[1]</sup> among which non-small cell lung cancer (NSCLC) account for the majority of all cases. The mutation rate of Epidermal Growth Factor Receptor (EGFR) varies across different ethnicities, and Asians have the highest mutation rate among all ethnicities.<sup>[2]</sup> During the last decades, EGFR Tyrosine Kinase Inhibitors (EGFR-TKIs) have changed the strategy of treatment and prolonged the progression-free survival (PFS) among patients harboring EGFR mutations.<sup>[3]</sup> However, drug resistance inevitably emerges<sup>[4]</sup> and becomes the major challenge of clinical work. Therefore, it is urgent to identify prognostic factors can predict target therapy efficacy.

Growing evidence shows inflammation plays a critical role in tumorigenesis and progression of cancer, and inflammation also affects immune surveillance and responses to therapy.<sup>[5]</sup> A few immune-inflammation based indicators have been studied as prognostic indicators in solid cancers, such as neutrophil-to-lymphocyte ratio (NLR)<sup>[6]</sup> and platelet-to-lymphocyte ratio (PLR).<sup>[7]</sup> Besides, immune cells and inflammatory proteins such

as albumin (Alb) and fibrinogen (Fib) have different expressions in cancer patients.<sup>[8,9]</sup> Alb and Fib are routinely tested to evaluate nutritional, inflammatory and coagulation status. However, the prognostic value of fibrinogen-albumin ratio index (FARI) in EGFR-Mutant advanced NSCLC patients treated with EGFR-TKI has been rarely reported.

In the present study, a cohort of 194 advanced lung adenocarcinoma patients carrying EGFR mutations were retrospectively analyzed to evaluate the clinical significance and prognostic value of NLR, PLR, and FARI in NSCLC patients receiving EGFR-TKI treatment.

## 2. Patients and methods

### 2.1. Patients

Patients harboring EGFR driven mutations pathological diagnosed as lung adenocarcinoma from January 2016 to December 2018 were collected at the Second Xiangya Hospital in Changsha, China. Patients in our study underwent first generation EGFR-TKI (gefitinib, erlotinib, or icotinib) as the first-line treatment, and blood test was taken within 1 week prior to the treatment. Patients with history of other malignant tumors, chronic inflammatory diseases, recent steroid therapy, acute infection or inflammation were excluded. Ethical approval was obtained from the Second Xiangya Hospital, Central South University.

### 2.2. Data collection

The clinical demographics (including age, gender, etc), smoking history, brain metastasis status, Eastern Cooperative Oncology Group (ECOG) score, EGFR mutation status and blood routine test, and blood biochemistry records were obtained from the electronic medical record system of the Second Xiangya Hospital. The FARI, NLR, and PLR were calculated as follows: FARI = fibrinogen / albumin; NLR = neutrophil counts / lymphocyte counts, PLR = platelet counts / lymphocyte counts. performance status (ECOG PS) was used to evaluate the physical status (on a scale of 0 to 5, with higher scores indicating a deteriorated general condition). The PFS was calculated from the date of diagnosis to the date of disease progression based on response evaluation criteria in solid tumors 1.1, or death. The overall survival (OS) was calculated from the date of diagnosis to the date of death for any reason or to the last date of follow-up. The last follow-up occurred in March 1, 2020.

### 2.3. Statistical Methods

All the statistical analyses were performed using SPSS 20.0. Receiver operating characteristic curves were used to calculate the optimal cut-off value for FARI, NLR, and PLR. Survival analysis was performed using Kaplan–Meier method. Chi-square test and log-rank test were used to compare the baseline clinical characteristics and survival curves, respectively. The predictive factors for survival were evaluated by univariate and multivariate analyses via the Cox hazards regression analysis. All tests were 2-sided and  $P < .05$  was statistically significant.

## 3. Results

### 3.1. Patient characteristics

Based on the inclusion criteria, 194 advanced lung adenocarcinoma patients with EGFR mutations were enrolled. The

**Table 1**

**clinicopathological characteristics of patients.**

Characteristics	Number (%)
Age	
Median	60
Range	28-88
Gender	
Male	88 (45.4%)
Female	106 (54.6%)
Smoking status	
Non-smoker	137 (70.6%)
Current or ex-smoker	57 (29.4%)
ECOG PS	
0-1	156 (80.4%)
2	38 (19.6%)
Brain metastasis	
Yes	24 (12.4%)
No	170 (87.6%)
EGFR Mutation	
L858R	79 (40.7%)
19-DEL	108 (55.7%)
Other	7 (3.6%)

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

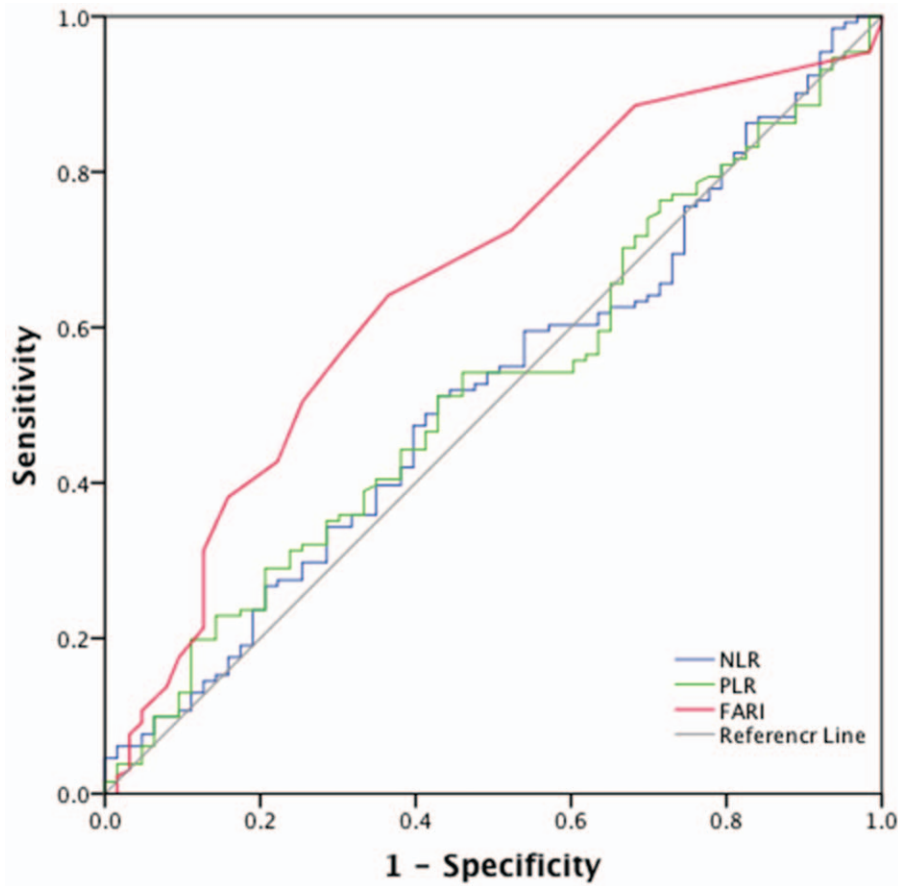
characteristics are shown in Table 1. The mean age of all enrolled patients was 60 with the range of 28 to 88 years, and 88 (45.4%) patients were male. 57 patients (29.4%) had a smoking history. This is consistent with the epidemiological pattern that the EGFR mutation rate is higher in females and non-smokers. The majority (156, 80.4%) had an ECOG score of 0 to 1. There were 24 patients with brain metastasis, and 5 patients received whole brain radiation therapy (WBRT) concurrent with TKI. Among all the patients, 79 (40.7%) patients carried L858R mutation in exon 21, 108 (55.7%) had exon 19 deletion mutation, and 7 (3.6%) had other rare mutations.

### 3.2. Cut-off value of FARI, NLR, PLR, and the association with clinical characteristics

Receiver operating characteristic analysis was used to get the cut-off value of FARI, NLR, PLR. As shown in Figure 1, the area under the curve for PFS were 0.659, 0.517, and 0.522. The optimal cutoff values of FARI, NLR, and PLR were 0.08, 3.28 and 273.85 for the prediction of PFS. The comparison of clinical characteristics between different groups in terms of FARI, NLR, and PLR is shown in Table 2. Patients with high FARI or NLR were more likely to have worse ECOG PS score ( $P = .018, .002$ , respectively). There were more males in high NLR patients compared with low NLR group ( $P = .043$ ). Other factors, including age, smoking status, brain metastasis, and EGFR mutation status are balanced between High/Low FARI, High/Low NLR, and High/Low PLR groups. It means that when testing the prognosis of FARI, NLR and PLR on patients' prognosis, all these factors are not confounding factors.

### 3.3. Univariate and multivariate Cox regression analysis for PFS and OS

Univariable analyses showed that the ECOG PS status, NLR, PLR and FARI were significantly associated with PFS ( $P = .017, .004, < .001, .001$ , respectively, Fig. 2) as well as OS ( $P < .001, = .001, .002, .023$ , respectively, Fig. 3), while other clinical

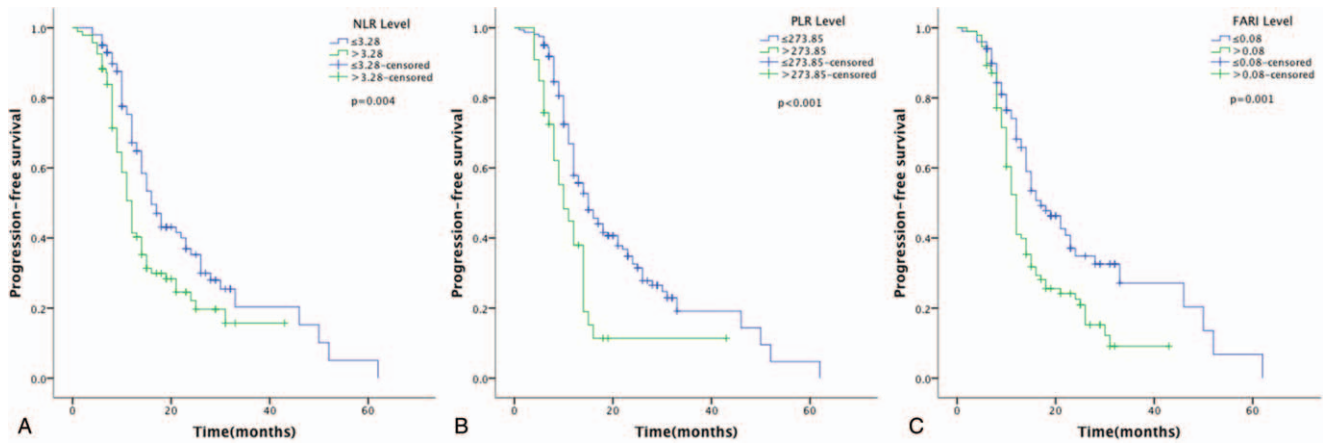


**Figure 1.** Receiver operating characteristic curve analysis for optimal cut-off value of NLR, PLR, and FARI for PFS. FARI = fibrinogen-albumin ratio index, NLR = neutrophil to lymphocyte ratio, PFS=progression free survival, PLR=platelet to lymphocyte ratio.

**Table 2**  
**Clinicopathological characteristics according to FARI, NLR and PLR.**

Characteristics	FARI high	FARI low	P	NLR high	NLR low	P	PLR high	PLR low	P
Age									
<65	62 (32.0%)	79 (40.7%)	.078	65 (33.5%)	76 (39.2%)	.334	28 (14.4%)	113 (50.3%)	.091
≥65	31 (16.0%)	22 (11.3%)		29 (14.9%)	24 (12.2%)		5 (2.6%)	48 (24.7%)	
Gender									
Male	44 (22.7%)	44 (22.7%)	.666	50 (25.8%)	38 (19.6%)	.043	15 (7.7%)	73 (37.6%)	1.000
Female	49 (25.3%)	57 (29.4%)		44 (22.7%)	62 (32.0%)		18 (9.3%)	88 (45.4%)	
Smoking status									
No	68 (35.1%)	69 (35.6%)	.529	66 (34.0%)	71 (36.6%)	1.000	25 (12.9%)	112 (57.7%)	.536
Yes	25 (12.9%)	32 (16.5%)		28 (14.4%)	29 (14.9%)		8 (4.1%)	49 (25.3%)	
ECOG PS									
0-1	68 (35.1%)	88 (45.5%)	.018	67 (34.5%)	89 (45.9%)	.002	23 (11.9%)	133 (68.6%)	.096
2	25 (12.9%)	13 (6.7%)		27 (13.8%)	11 (5.7%)		10 (5.2%)	28 (14.4%)	
Brain metastasis									
Yes	14 (7.2%)	10 (5.2%)	.286	11 (5.7%)	13 (6.7%)	.830	5 (2.6%)	19 (9.8%)	.568
No	79 (40.7%)	91 (46.9%)		83 (42.8%)	87 (44.8%)		28 (14.4%)	142 (73.2%)	
EGFR Mutation									
L858R	43 (22.2%)	36 (18.6%)	.091	39 (20.1%)	40 (20.6%)	.183	11 (5.7%)	68 (35.1%)	.243
19-DEL	49 (25.3%)	595 (30.4%)		54 (27.8%)	54 (27.8%)		22 (11.3%)	86 (44.3%)	
Other	1 (0.5%)	6 (3.1%)		1 (0.5%)	6 (3.1%)		0 (0.9%)	7 (3.6%)	

ECOG PS=Eastern Cooperative Oncology Group Performance Status, FARI=fibrinogen-albumin ratio index, NLR = neutrophil to lymphocyte ratio, OS=overall survival, PFS=progression free survival, PLR=platelet to lymphocyte ratio.



**Figure 2.** Kaplan–Meier curves of PFS according to NLR(A), PLR(B), and FARI(C). PFS=progression free survival, NLR=neutrophil to Lymphocyte Ratio, PLR=platelet to lymphocyte ratio, FARI=fibrinogen-albumin ratio index.

characteristics including age, gender, smoking status, brain metastasis or mutation types showed no statistically significance in the present analysis (Table 3).

In the multivariate Cox regression analysis, PLR (hazard ratios [HR] 1.692; 95% CI 1.054–2.715;  $P=.029$ ) and FARI (HR 1.496; 95% CI 1.031–2.172;  $P=.034$ ) were independent prognostic factors for PFS. While only ECOG PS status (HR 2.052; 95% CI 1.272–3.310;  $P=.003$ ) was identified as independent predictor of OS in patients receiving EGFR-TKIs as first-line treatment for advanced lung adenocarcinoma (Table 4).

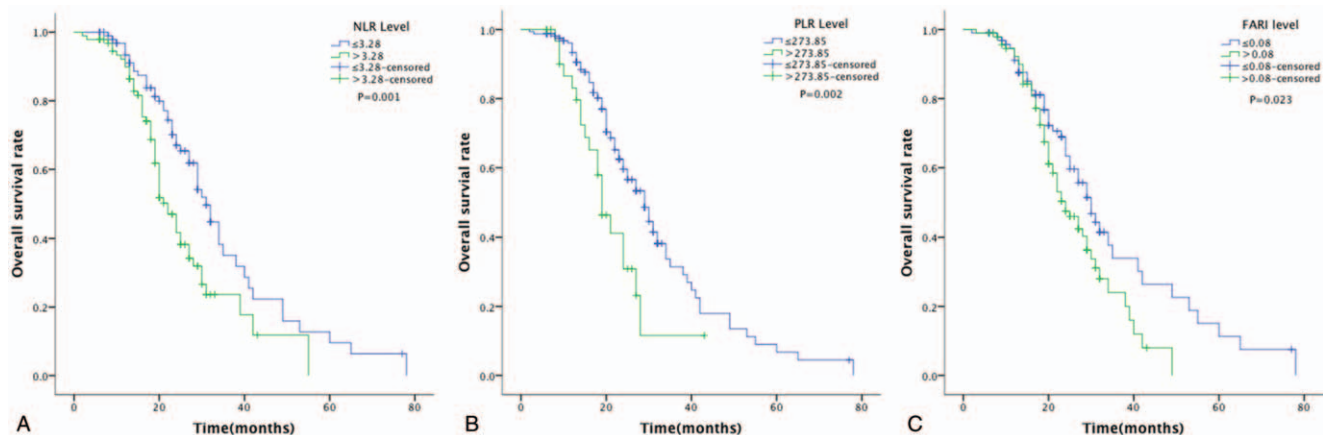
#### 4. Discussion

We evaluated the prognostic value of immune-inflammation factors, FARI, NLR, and PLR which could be obtained from blood test before treatment, in advanced lung adenocarcinoma patients with EGFR mutations. The clinical characteristics showed patients with  $FARI \geq 0.08$  or  $NLR \geq 3.28$  were more likely to have worse ECOG PS scores, and there were more males in the NLR high group than controls. Further, the pretreatment FARI and PLR were independent prognostic factors for PFS,

while only ECOG PS score could independently suggest prognosis for OS in the present study.

Inflammation is a recognized hallmark of cancer.<sup>[10]</sup> Increasing evidence shows inflammatory responses is involved in different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis, and inflammation also affects immune surveillance and responses to therapy.<sup>[5]</sup> Tumor cells could secrete pro-inflammatory factors, and systemic inflammation could in return promote tumor cell proliferation, angiogenesis, and inhibit host anti-tumor immune response.<sup>[11]</sup> Systemic inflammation is widely evidenced by a number of markers at clinical thresholds across tumor types and geographical locations, and patients with inflammation were more likely to have a worse prognosis.<sup>[12]</sup> Well-established inflammation-based indicators, such as NLR<sup>[6]</sup> and PLR,<sup>[7]</sup> have been reported to be associated with prognosis in various cancers.

Fibrinogen, an important protein in coagulation process, also possess pro-inflammatory activity, and has been reported to play roles in tumor progression.<sup>[13]</sup> The development of cancer induces a host response, and inflammatory mediators are secreted and disturb the hemostatic balance, leading to the increase of the blood pro-thrombotic potential. Plasma fibrinogen contributes to



**Figure 3.** Kaplan–Meier curves of OS according to NLR(A), PLR(B), and FARI(C). OS=overall survival, NLR=neutrophil to lymphocyte ratio, PLR=platelet to lymphocyte ratio, FARI=fibrinogen-albumin ratio index.

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

Variables	PFS			OS		
	case	MST (m)	P	case	MST (m)	P
Age						
<65	141	14 ± 0.80	.299	141	27 ± 1.97	.596
≥65	53	18 ± 5.59		53	31 ± 5.76	
Gender						
Male	88	12 ± 1.15	.560	88	24 ± 1.79	.276
Female	106	14 ± 0.69		106	29 ± 2.30	
Smoking status						
No	137	14 ± 0.72	.274	137	29 ± 2.33	.226
Yes	57	12 ± 1.52		57	24 ± 1.26	
ECOG PS						
0-1	156	17 ± 0.88	.017	156	29 ± 1.44	<.001
2	38	11 ± 0.94		38	19 ± 1.31	
Brain metastasis						
Yes	24	11 ± 0.93	.453	24	24 ± 1.84	.82
No	170	14 ± 0.99		170	27 ± 2.11	
EGFR Mutation						
L858R	79	12 ± 1.18	.233	79	22 ± 2.88	.087
19-DEL	108	15 ± 1.04		108	28 ± 1.87	
Other	7	12 ± 1.96		7	NR	
NLR						
High	94	12 ± 0.61	.004	94	22 ± 1.46	.001
Low	100	16 ± 1.42		100	31 ± 1.87	
PLR						
High	33	10 ± 1.76	<.001	33	19 ± 1.71	.002
Low	161	15 ± 1.43		161	29 ± 1.97	
FARI						
High	93	12 ± 0.54	.001	93	24 ± 2.10	.023
Low	101	17 ± 2.40		101	30 ± 2.34	

ECOG PS=Eastern Cooperative Oncology Group Performance Status, FARI=fibrinogen-albumin ratio index, MST=median survival time, NLR=neutrophil to lymphocyte ratio, OS=overall survival, PFS=progression free survival, PLR=platelet to lymphocyte ratio.

metastasis by promoting adhesion and survival of tumor cells after invasion in lung cancer mouse model.<sup>[14]</sup> Albumin is routinely tested in cancer patients before treatment. Albumin synthesis is suppressed in the later stages of disease, malnutrition and inflammation. Inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$  and IL-6 suppressed synthesis of albumin, leading to hypoproteinemia in NSCLC patients.<sup>[15]</sup> A

Systematic Review reported higher serum albumin levels was associated with better survival in lung cancer in 9 out of 10 studies.<sup>[16]</sup>

FARI is a better indicator since it can comprehensively reflect inflammation and nutrition status compared with plasma fibrinogen or albumin alone. Previous studies have demonstrated prognostic value of FARI and its superiority over NLR and PLR

**Table 4****Multivariable Cox regression analyses for PFS and OS.**

Variables	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
ECOG PS				
High	1.343 (0.869-2.074)	.184	2.052 (1.272-3.310)	.003
Low				
NLR				
High	1.252 (0.848-1.847)	.258	1.487 (0.961-2.301)	.075
Low				
PLR				
High	1.692 (1.054-2.715)	.029	1.556 (0.911-2.656)	.105
Low				
FARI				
High	1.496 (1.031-2.172)	.034	1.264 (0.832-1.922)	.273
Low				

FARI=fibrinogen-albumin ratio index, NLR=neutrophil to lymphocyte ratio, OS=overall survival, PFS=progression free survival, PLR=platelet to lymphocyte ratio.

in non-small cell lung cancer<sup>[17,18]</sup> and colorectal cancer.<sup>[19]</sup> Li SQ, et al<sup>[17]</sup> found that clinical outcome of high albumin-to-fibrinogen ratio AFR (>7.3) in stage II–III NSCLC patients undergoing chemo-radiotherapy was significantly superior to the low AFR cases. Another research in advanced NSCLC patients undergoing first-line platinum-based chemotherapy reported that patients with high AFR (>8.02) has significantly improved PFS and OS compared with low AFR group.<sup>[18]</sup>

Nowadays, the treatment of lung cancer is multimodality comprehensive treatment, including surgery, chemotherapy, radiation therapy, target therapy, and immunotherapy. Previous studies about immune and inflammation indicators in NSCLC mainly focused on patients receiving resection, chemotherapy and radiation therapy. Reports on the prognostic role of those indicators in EGFR-mutant NSCLC patients receiving EGFR-TKI as first-line treatment is rare. Aguiar-Bujanda D et al reported NLR is an independent prognostic factor for OS in Western European patients with EGFR-mutant NSCLC treated with EGFR-TKIs.<sup>[20]</sup> Previously our group has demonstrated that systemic immune-inflammation index (SII) is an independent prognostic factor for poor survival in advanced EGFR-Mutant lung adenocarcinoma patients treated with first-generation TKIs.<sup>[21]</sup> In the present study, for the first time the prognostic value of FARI is evaluated in the EGFR-mutant population, we found FARI was and independent prognostic factors for PFS (HR 1.496; 95% CI 1.031–2.172;  $P=.034$ ).

In our study, FARI, as well as PLR, were independent prognostic factors for PFS, which is partially consistent with previous study in lung cancer. We haven't got a statistically significant difference of FARI in predicting OS. As multimodality comprehensive treatment for lung cancer is available, the different choices in following lines treatment makes it hard to computation.

Studies about therapeutic strategies focusing on inflammation and mal-nutrition may provide new insights to suppress tumor progression and improve the prognosis of cancer patients. A clinical trial using traditional Chinese medicine reported that the wheat-size moxibustion therapy reduced NLR and improved the immune function and quality of life in the patients of NSCLC.<sup>[22]</sup> Cachexia is a complication of cancer, especially in advanced stage, whose major manifestation is loss of muscle and fat mass, and is correlated with shorter survival and worse quality-of-life.<sup>[23]</sup> A research in rats showed the reversal of cancer cachexia could prolong survival.<sup>[24]</sup> A clinical trial in NSCLC patients with cachexia demonstrated anamorelin could improve body weight and anorexia-cachexia symptoms.<sup>[25]</sup> Further studies in researches and even clinical practice, on effective interventions based on inflammation and mal-nutrition in cancer is needed.

There is obviously limitation of this study. This was a single center retrospective study with a comparably small sample size. The number of patients with brain metastasis and ECOG PS score of >2 was small, thus the imbalance between groups may bring some bias. Further prospective studies with a multiple-central design and large sample size is warranted to validate the role of the FARI in predicting clinical efficacy in EGFR-mutant NSCLC receiving first-line EGFR-TKIs treatment.

In conclusion, FARI, a simple, economical biomarker which reflect the inflammation and nutrition status, is independently associated with PFS in EGFR-Mutant lung adenocarcinoma patients receiving first-line EGFR-TKIs treatment, and it worth further research to confirm the prognostic value in clinical practice.

## Author contributions

**Conceptualization:** Tao Hou.

**Data curation:** Xiayan Zhao, Na Zhang, Haixia Zhang.

**Investigation:** Xiayan Zhao, Na Zhang, Haixia Zhang, Ping Liu, Fang Wu.

**Methodology:** Xiayan Zhao, Tao Hou, Chunhong Hu, Xianling Liu.

**Resources:** Tao Hou.

**Supervision:** Chunhong Hu, Xianling Liu.

**Writing – original draft:** Xiayan Zhao.

**Writing – review & editing:** Ping Liu, Jinan Ma, Chunhong Hu, Xianling Liu, Tao Hou.

## References

- [1] Torre LA, Siegel RL, Jemal A. Lung cancer statistics. *Adv Exp Med Biol* 2016;893:1–9.
- [2] Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014;9:154–62.
- [3] Normando SR, Cruz FM, Del Giglio A. Cumulative meta-analysis of epidermal growth factor receptor-tyrosine kinase inhibitors as first-line therapy in metastatic non-small-cell lung cancer. *Anticancer Drugs* 2015;26:995–1003.
- [4] Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
- [5] Grivnickov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;140:883–99.
- [6] Yao JJ, Zhu FT, Dong J, et al. Prognostic value of neutrophil-to-lymphocyte ratio in advanced nasopharyngeal carcinoma: a large institution-based cohort study from an endemic area. *BMC Cancer* 2019;19:37.
- [7] Vernieri C, Mennitto A, Prisciandaro M, et al. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict efficacy of platinum-based chemotherapy in patients with metastatic triple negative breast cancer. *Sci Rep* 2018;8:8703.
- [8] Balkwill F, Mantovani A. Inflammation and cancer: back to virchow? *Lancet* 2001;357:539–45.
- [9] Ghezzi F, Cromi A, Siesto G, et al. Prognostic significance of preoperative plasma fibrinogen in endometrial cancer. *Gynecol Oncol* 2010;119:309–13.
- [10] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.
- [11] Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014;15:493–503.
- [12] Dolan RD, McSorley ST, Horgan PG, et al. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2017;116:134–46.
- [13] Kołodziejczyk J, Ponczek MB. The role of fibrinogen, fibrin and fibrin (ogen) degradation products (FDPs) in tumor progression. *Contemp Oncol* 2013;17:113–9.
- [14] Palumbo JS, Kombrinck KW, Drew AF, et al. Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. *Blood* 2000;96:3302–9.
- [15] Rothschild MA, Oratz M, Schreiber SS. Serum albumin. *Hepatology* 1988;8:385–401.
- [16] Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J* 2010;9:69.
- [17] Li SQ, Jiang YH, Lin J, et al. Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals. *Cancer Med* 2018;7:1221–31.
- [18] Ying J, Zhou D, Gu T, et al. Pretreatment albumin/fibrinogen ratio as a promising predictor for the survival of advanced non small-cell lung cancer patients undergoing first-line platinum-based chemotherapy. *BMC Cancer* 2019;19:288.
- [19] Wang Y, Liu Z, Xu D, et al. Fibrinogen–albumin ratio index (FARI): a more promising inflammation-based prognostic marker for patients

- undergoing hepatectomy for colorectal liver metastases. *Ann Surg Oncol* 2019;26:3682–92.
- [20] Aguiar-Bujanda D, Duenas-Comino A, Saura-Grau S, et al. Neutrophil to lymphocyte ratio as a prognostic factor in european patients with epidermal growth factor receptor-mutant non-small cell lung cancer treated with tyrosine kinase inhibitors. *Oncol Res Treat* 2018;41:755–61.
- [21] 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* 2019;98:e16875.
- [22] Zhang M, Guan L. Impact on neutrophil-to-lymphocyte ratio and quality of life in the patients of non-small-cell lung cancer treated with grain-size moxibustion: a randomized controlled trial. *Zhongguo Zhen Jiu* 2016;36:342–6.
- [23] Meij BS, van der , Schoonbeek CP, et al. Pre-cachexia and cachexia at diagnosis of stage III non-small-cell lung carcinoma: an exploratory study comparing two consensus-based frameworks. *Br J Nutr* 2013;109:2231–9.
- [24] Zhou X, Wang JL, Lu J, et al. Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell* 2010;142:531–43.
- [25] Currow D, Temel JS, Abernethy A, et al. ROMANA 3: a phase 3 safety extension study of anamorelin in advanced non-small-cell lung cancer (NSCLC) patients with cachexia. *Ann Oncol* 2017;28:1949–56.