Received: 4 January 2022 | Accepted: 22 February 2022

DOI: 10.1111/1759-7714.14380

ORIGINAL ARTICLE

WILEY

Establishment of prognostic nomograms for predicting the progression free survival of EGFR-sensitizing mutation, advanced lung cancer patients treated with EGFR-TKIs

Xinyang Du | Hua Bai | Zhijie Wang | Jianchun Daun | Zheng Liu | Jiachen Xu | Geyun Chang | Yixiang Zhu | Jie Wang

State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence
Jie Wang, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.
Email: zlhuxi@163.com

Funding information
Aiyou foundation, Grant/Award Number: KY201701; Beijing Hope Run Special Fund of Cancer Foundation of China, Grant/Award Number: LC2020B09 to Dr. Jiachen Xu; National key research and development project, Grant/Award Number: 2019YFC1315700; NSFC general program, Grant/Award Numbers: 81871889, 81972905; NSFC key program, Grant/Award Number: 81630071; the Special Research Fund for Central Universities, Peking Union Medical College, Grant/Award Number: 3332021029 to Dr. Jiachen Xu; Peking Union Medical College; Special Research Fund

Abstract

Background: There is a lack of clinically available predictive models for patients with epidermal growth factor receptor (EGFR) mutation positive, advanced non–small cell lung cancer (NSCLC) treated with EGFR-tyrosine kinase inhibitors (TKIs).

Methods: The clinical data of patients at the Cancer Hospital, Chinese Academy of Medical Sciences between from January 2016 to January 2021 were retrospectively retrieved as training set. The patients from BENEFIT trial were for the validation cohort. The nomogram was built based on independent predictors identified by univariate and multivariate Cox regression analyses. The discrimination and calibration of the nomogram were evaluated by C-index and calibration plots.

Results: A total of 502 patients with complete clinical data and follow-up information were enrolled in this study. Five independent prognostic factors, including The Eastern Cooperative Oncology Group Performance Status scale (ECOG PS), EGFR mutation subtype, EGFR co-mutation, liver metastasis and malignant pleural effusion ($p < 0.05$). The C-indexes of the nomogram were 0.694 (95% confidence interval [CI], 0.663–0.725) for the training set and 0.653 (95% CI, 0.610–0.696) for the validation set. The calibration curves for the probabilities of 9-, 12- and 18-month progression-free survival (PFS) revealed satisfactory consistency in both the internal and external validations. Additionally, the patients were divided into two groups according to risk (high-risk, low-risk), and significant differences in PFS were observed between the groups in the training and external validation cohorts ($p < 0.001$).

Conclusions: We constructed and validated a convenient nomogram that have the potential to become an accurate and reliable tool for patients with EGFR mutation positive, advanced NSCLC to individually predict their potential benefits from EGFR-TKIs, and facilitate clinical decision-making.

KEYWORDS
advanced non–small cell lung cancer, EGFR-sensitizing mutation, nomogram, prognosis, progression free survival

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide, and non–small cell lung cancer (NSCLC) accounts for ~85% of the total number of reported cases.[1] In recent decades, lung cancer incidence and mortality have overtly increased and it has become a major cause of death in China.[2] Epidermal growth factor receptor (EGFR) mutations account for a considerable proportion of NSCLC, especially among women, non-smokers, East Asians, and adenocarcinoma patients.[3] Among the types of EGFR mutations, exon 19 deletion (19del) mutation and exon 21 (L858R) point mutation are

the two classic mutations, accounting for 90% of all EGFR mutation patients.[4] During the past decade, given that patients with EGFR-mutant-driven tumors achieve benefit from EGFR tyrosine kinase inhibitors (TKIs), their treatment mode has transitioned from cytotoxicity to targeted therapy. Currently, multiple generations of EGFR-TKIs have been developed and established as a standard first-line treatment.[5–9]

Findings from previous randomized phase 3 studies done in the genetically selected patients with lung cancer have shown differences in progression-free survival (PFS) with EGFR-TKIs based on EGFR mutation subtype; progression-free survival was most improved in patients with tumor harboring 19del followed by 21L858R mutation.[10] With these developments, these two common EGFR mutations are considered independent, and the ideal treatment model is currently being explored.[11] Otherwise, a novel subclassification strategy based on baseline co-mutation status (stratified by tumor suppressor genes and oncogenic genes) was proposed, which showed that the patients with concomitant mutations had the shorter PFS and overall survival (OS).[12] However, with the exception of molecular subclassification, the predictive or prognostic relevant factors of EGFR-TKIs have not been well integrated. Previous studies have used relevant variables to establish models to predict clinical outcomes, but lack of Asian population data and external validation makes them unsuitable to guide current clinical practice.[13] Currently, there is no available tool that can integrate multiple putative prognostic factors into a single numeric estimate of survival of lung adenocarcinoma patients receiving naive treatment with EGFR-TKIs.

Nomogram that integrates clinical, pathological, and other variable information has been widely used to predict the survival of cancer patients.[14–15] Therefore, this study aimed to establish a nomogram for predicting PFS for EGFR-TKIs in patients with NSCLC by combining pretreatment clinicopathological variables and molecular subclassification based on data from the real world.

METHODS

Patient characteristics

A total of 3141 patients diagnosed with lung cancer and treated with target therapy were enrolled from the Cancer Hospital,

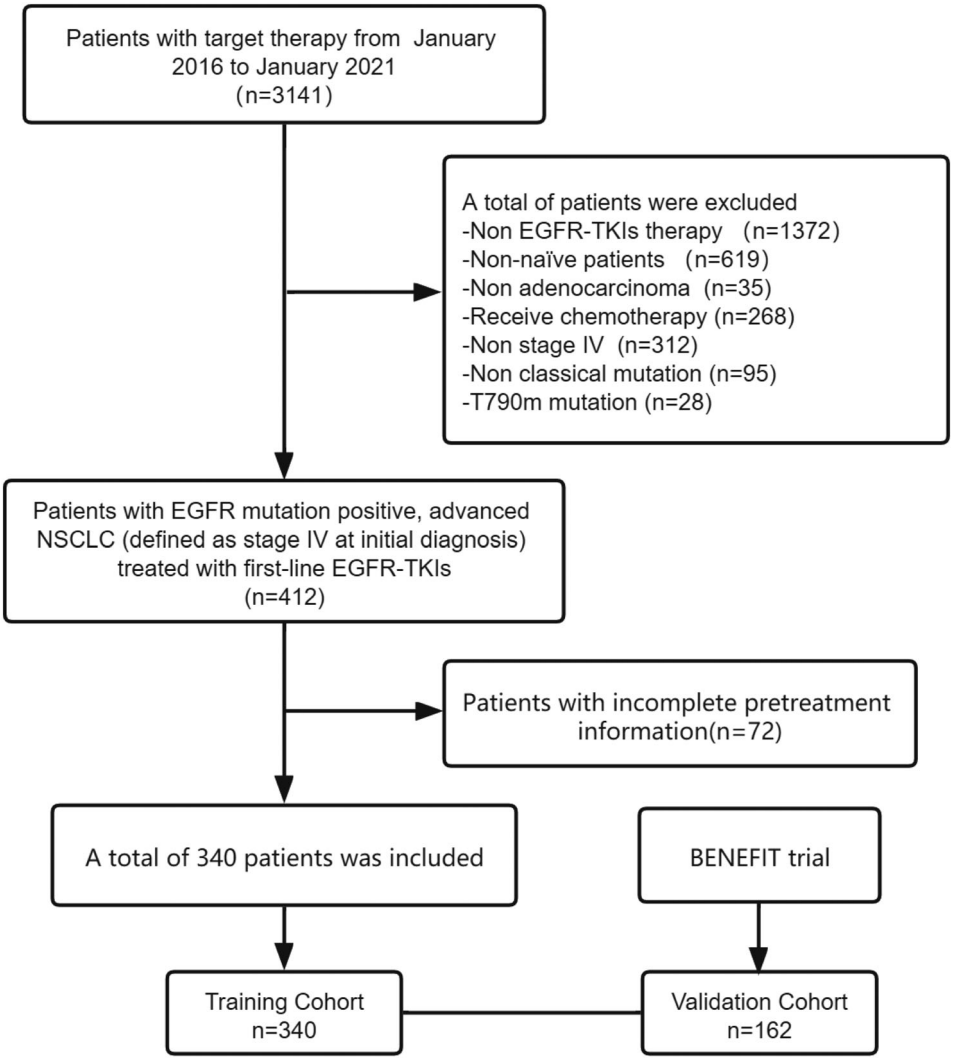

FIGURE 1 Flow chart of the study population selection

Chinese Academy of Medical Sciences January 2016 to January 2021. The inclusion criteria were as follows: (1) age over 18 years old; (2) patients who were diagnosed by histopathology or cytopathology as lung adenocarcinoma; (3) stage IV NSCLC at initial diagnosis (according to the 8th American Joint Committee on Cancer Staging System); (4) EGFR-sensitizing mutations (EGFR 19del or EGFR 21L858R) and EGFR co-mutation (oncogenic drivers and tumor-suppressor genes) detected by next generation sequencing (NGS) or droplet digital polymerase chain reaction (ddPCR) in pretreatment tissue or plasma; (5) received first-line EGFR-TKIs therapy (no previous chemotherapy, immunotherapy, or other systemic anticancer treatment); (6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score at 0–2. The main exclusion criteria were: (1) presence of histologically confirmed squamous and adenosquamous carcinoma or other co-existing malignant disease; (2) patients with incomplete clinical data and follow-up information. The external validation cohort consisted of 162 patients from an open-label, single-arm, prospective, multicenter, phase 2 clinical trial (BENEFIT trial).

Data collection

We collected the demographic and clinical features from medical records: gender, age, smoking status (never/former/current), ECOG PS (0–1/2), EGFR mutation subtype (EGFR 19del or EGFR 21L858R), EGFR co-mutation (oncogenic drivers and tumor-suppressor genes), liver metastasis, brain metastasis, bone metastasis, malignant pleural effusion, and number of metastasized organs (<4/≥4). At baseline, patients had to have at least one lesion (10 mm in the longest diameter in non-lymph-node lesions, or short axis >15 mm in lymph nodes), not previously irradiated, that could be measured by computed tomography (CT) or magnetic resonance imaging (MRI), and suitable for repeated measurement. Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 with CT or MRI. PFS was defined as the start of treatment with EGFR-TKIs to disease progression or death.[16] The last follow-up time was November 20, 2021.

Statistical analysis

PFS was assessed using the Kaplan–Meier method and compared using the log-rank test. The correlations between clinicopathological characteristics and PFS were estimated by Cox proportional hazards regression models. Variables with statistical differences in the univariable Cox regression analysis were incorporated into the multivariable regression model. Based on the multivariate model, a nomogram was constructed to generate survival probability at 9-month, 12-month, 18-month, and median PFS time after treatment of EGFR-TKIs.

The nomogram performs bootstrap internal verification in the training cohort and external verification using the verification cohort. The performance of the nomogram was evaluated by the receiver operating characteristics (ROC). C-index and calibration curve are used to evaluate the accuracy of the nomogram, with 0.5 indicating a random result, 1.0 indicating that the model can predict the prognostic result completely and correctly. Decision curves analysis (DCA) was used to assess the net benefit of a nomogram for clinical decision making at different threshold probabilities.

TABLE 1 Baseline clinicopathological characteristics of the training and validation cohorts

Characteristic	Training cohort ($N = 340$)	Validation cohort ($N = 162$)
Gender no. (%)		
Male	138 (40.6)	72 (44.4)
Female	202 (59.4)	90 (55.6)
Age no. (%), y		
<65	239 (70.3)	117 (72.2)
≥65	101 (29.7)	45 (27.8)
Smoking status, no. (%)		
Never	238 (70.0)	122 (75.3)
Former/current	102 (30.0)	40 (24.7)
ECOG PS, no. (%)		
0–1	299 (87.9)	150 (92.6)
2	41 (12.1)	12 (7.4)
EGFR mutation subtype, no. (%)		
Exon 19 del	179 (52.6)	85 (52.5)
Exon 21 L858R	161 (47.4)	77 (47.5)
EGFR co-mutation, no. (%)		
No	281 (82.6)	54 (33.3)
Yes	59 (17.3)	108 (66.7)
Liver metastasis, no. (%)		
No	290 (85.3)	147 (90.7)
Yes	50 (14.7)	15 (9.3)
Brain metastasis, no. (%)		
No	221 (65.0)	108 (66.7)
Yes	119 (35.0)	54 (33.3)
Bone metastasis, no. (%)		
No	139 (40.9)	93 (57.4)
Yes	201 (59.1)	69 (42.6)
Malignant pleural effusion, no. (%)		
No	280 (82.4)	142 (87.7)
Yes	60 (17.6)	20 (12.3)
Number of metastasized organs, no. (%)		
<4	302 (88.8)	125 (77.2)
≥4	38 (11.2)	37 (22.8)

Note: EGFR mutation status was ctDNA-based. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor.

A total nomogram score was calculated for each patient and to generate risk strata (high-risk, low-risk). A Kaplan–Meier survival analysis with the log-rank test was performed to assess the significance of the survival difference between the three risk groups.

All statistical analyses were performed using the R software (Version 4.1.1; https://www.R-project.org). Two-sided $p < 0.05$ were considered as statistically significant.

RESULTS

Patients' characteristics

A total of 3141 patients diagnosed with lung cancer treated with target therapy were enrolled in the study. Of these, 2773 participants were excluded for not meeting the inclusion criteria. A further 72 cases were reviewed and excluded

TABLE 2 Univariate and multivariate Cox regression analysis of progression-free survival in the training cohort

	Univariable analysis		Multivariable analysis	
Characteristics	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Gender				
Male	Reference	0.410		
Female	1.100 (0.877, 1.379)			
Age, y				
<65	Reference	0.209		
≥65	1.171 (0.915, 1.497)			
Smoking status				
Never	Reference	0.178		
Former/current	1.180 (0.928, 1.500)			
ECOG PS				
0–1	Reference	<0.001	Reference	<0.001
2	3.497 (2.472, 4.946)		3.552 (2.487, 5.072)	
EGFR mutation subtype				
Exon 19 del	Reference	<0.001	Reference	<0.001
Exon 21 L858R	1.718 (1.368, 2.518)		1.802 (1.427, 2.275)	
EGFR co-mutation				
No	Reference	<0.001	Reference	0.036
Yes	1.730 (1.289, 2.323)		1.379 (1.021, 1.863)	
Liver metastasis				
No	Reference	0.002	Reference	0.007
Yes	1.632 (1.186, 2.245)		1.720 (1.153, 2.565)	
Brain metastasis				
No	Reference	0.715		
Yes	1.044 (0.827, 1.318)			
Bone metastasis				
No	Reference	0.775		
Yes	1.033 (0.826, 1.293)			
Malignant pleural effusion				
No	Reference	<0.001	Reference	<0.001
Yes	2.234 (1.670, 2.990)		2.041 (1.514, 2.752)	
Number of metastasized organs				
<4	Reference	<0.001	Reference	0.096
≥4	1.859 (1.312, 2.634)		1.441 (0.936, 2.218)	
EGFR-TKIs choice				
Third generation EGFR-TKI	Reference	0.064		
Second generation EGFR-TKIs	1.186 (0.640, 2.197)			
First generation EGFR-TKIs	1.488 (1.053, 2.105)			

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

because of incomplete pretreatment information, giving a final study population of 340 patients. Figure 1 is the flow chart of the study population. In the final inclusion population, there are 340 cases as the discovery set for predictive model establishment and 162 cases as the validation set (Table 1). In the training cohort, the average age at the time of diagnosis was 58.8 years old (range, 29–86), and 239 (77.9%) patients were <65 years old. With respect to stratification factors, most participants were female (59.4%), never smokers (70.0%), and had ECOG PS score 0–1 (87.9%). At the time of diagnosis, the most frequent metastatic locations were bone in 59.1%, brain in 35.0%, and malignant pleural effusion in 17.6% of cases. Of these patients, 179 (52.6%) had EGFR 19del mutation, and 161 (47.4%) had EGFR 21L858R mutation. Moreover, the proportion of patients receiving the first, second, and third generation EGFR-TKIs was 82.6%, 5%, and 12.4%, respectively. In the external validation cohort, 72 (44.4%) patients were male, and 117 (72.2%) patients were <65 years old. Among these patients, 85 (52.5%) had EGFR 19del mutation and 77 (47.5%) had EGFR 21L858R mutation.

Survival analyses

As the two most common types of EGFR mutations, EGFR-TKIs are associated with best PFS for patients with EGFR 19del. There were 472 disease progression events in this cohort, with a median PFS of 11.2 months in the EGFR 19del group and 8.5 months in the EGFR 21 L858R group (Figure S1; Table S1). Kaplan–Meier event curves showed separation between the two groups, and the conclusion was consistent with previous studies. Moreover, the patients harboring EGFR 21L858R were accompanied by a higher proportion of co-mutation than EGFR 19del (37.4% vs. 29.5%).

The results of univariate and multivariate Cox analyses in the training cohort are listed in Table 2. The univariate analysis

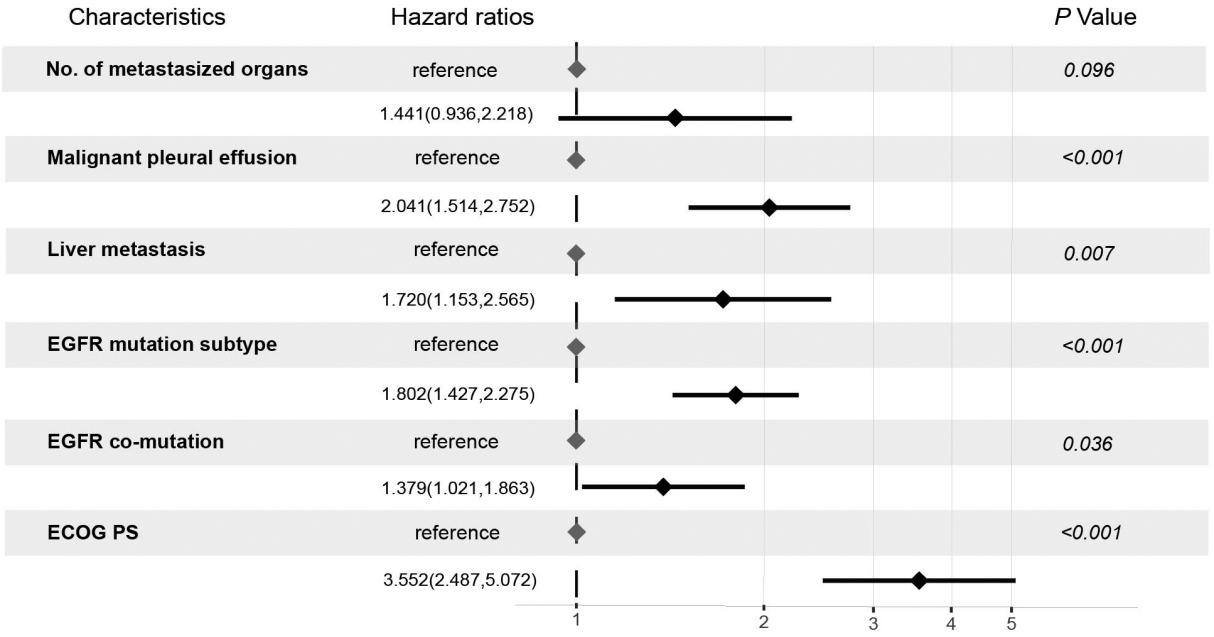

FIGURE 2 Multivariate Cox regression analysis of PFS in key subgroups

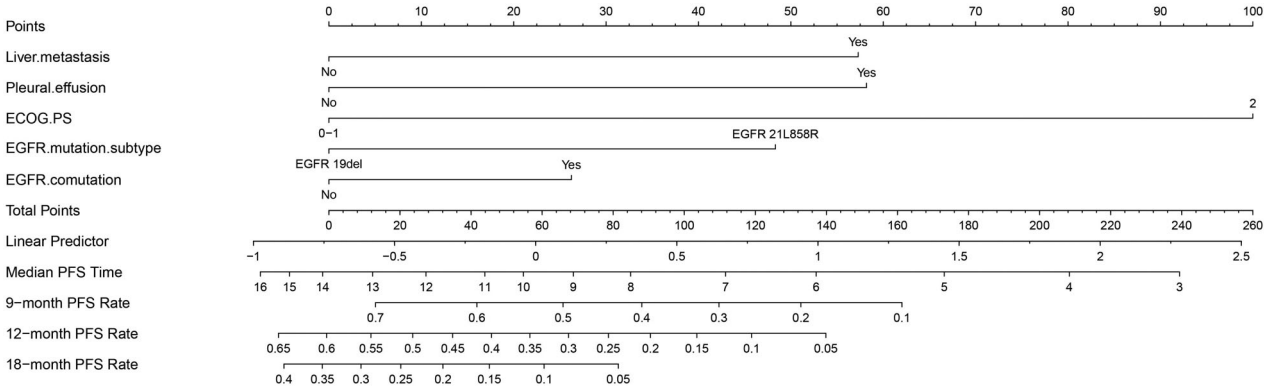

FIGURE 3 Nomogram to predict the 9-, 12-, 18-month PFS, and median PFS time

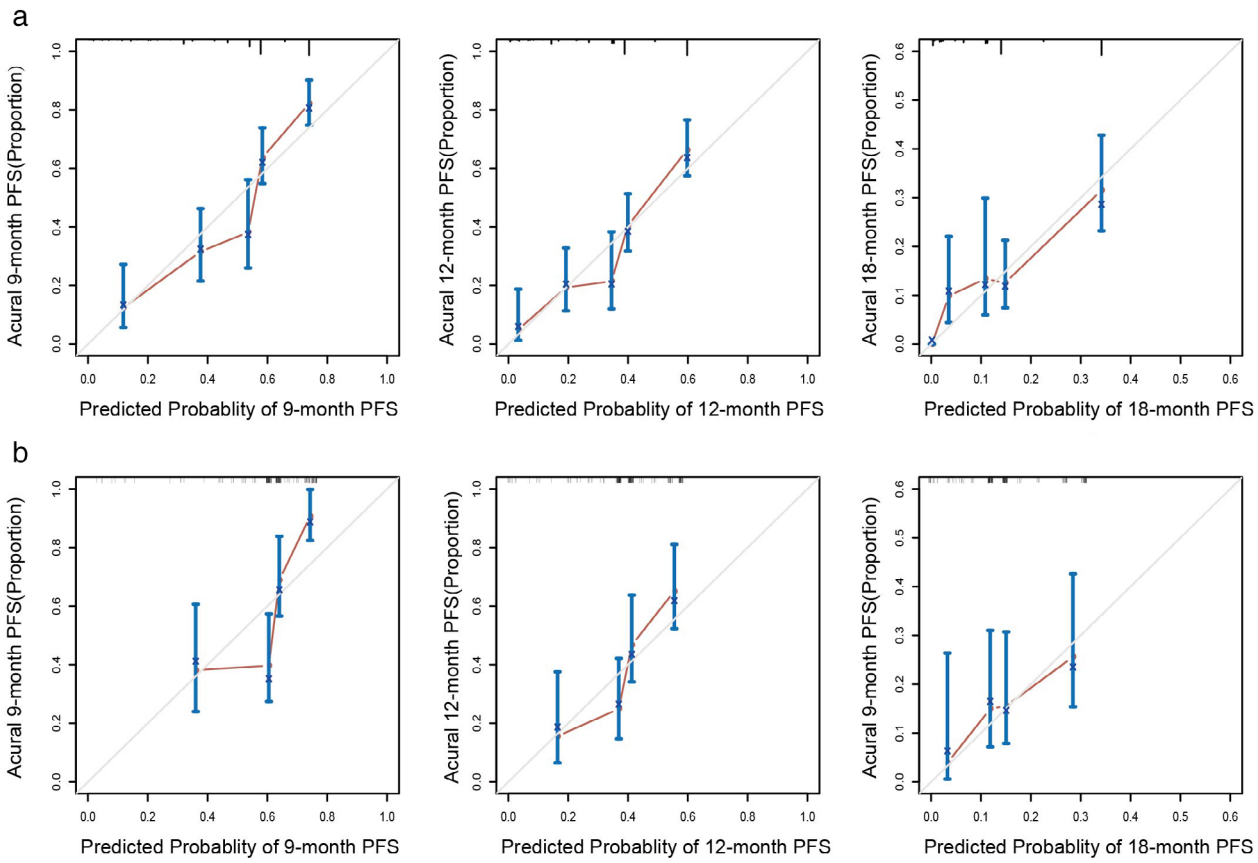

FIGURE 4 The calibration curves to predict the 9-, 12-, 18-month PFS in the training cohort (a), and validation cohort (b)

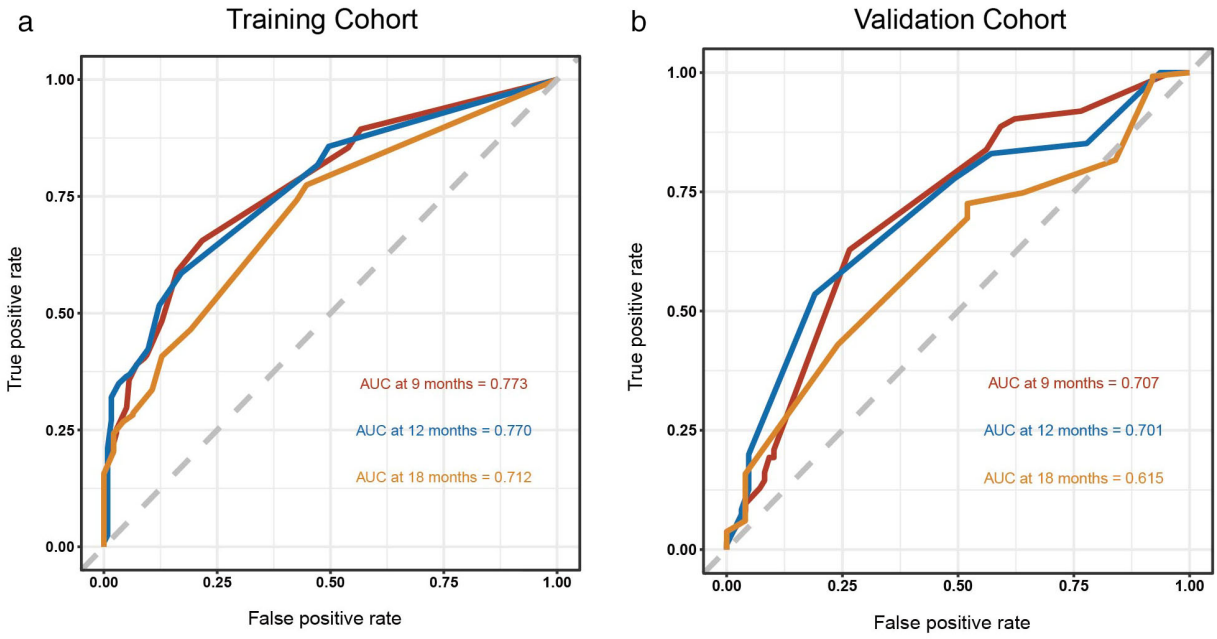

FIGURE 5 ROC curve of the nomogram in the training set (a) and testing set (b)

indicated that ECOG PS, EGFR mutation subtype, EGFR co-mutation, liver metastasis, malignant pleural effusion, and number of metastasized organs were significantly associated with PFS (Figure S2, $p < 0.05$). Based on the univariate analysis, the following five independent risk factors were selected for the multivariate analysis using a Cox regression: ECOG PS (≥2:hazard

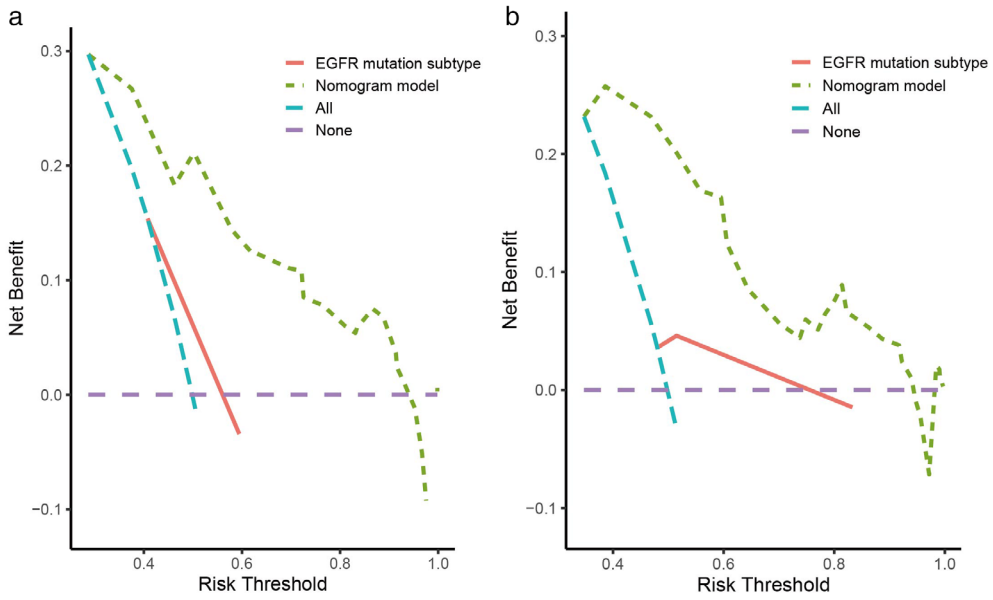

FIGURE 6 Decision curve analysis (DCA) for the nomogram of the training cohort (a) and the validation cohort (b)

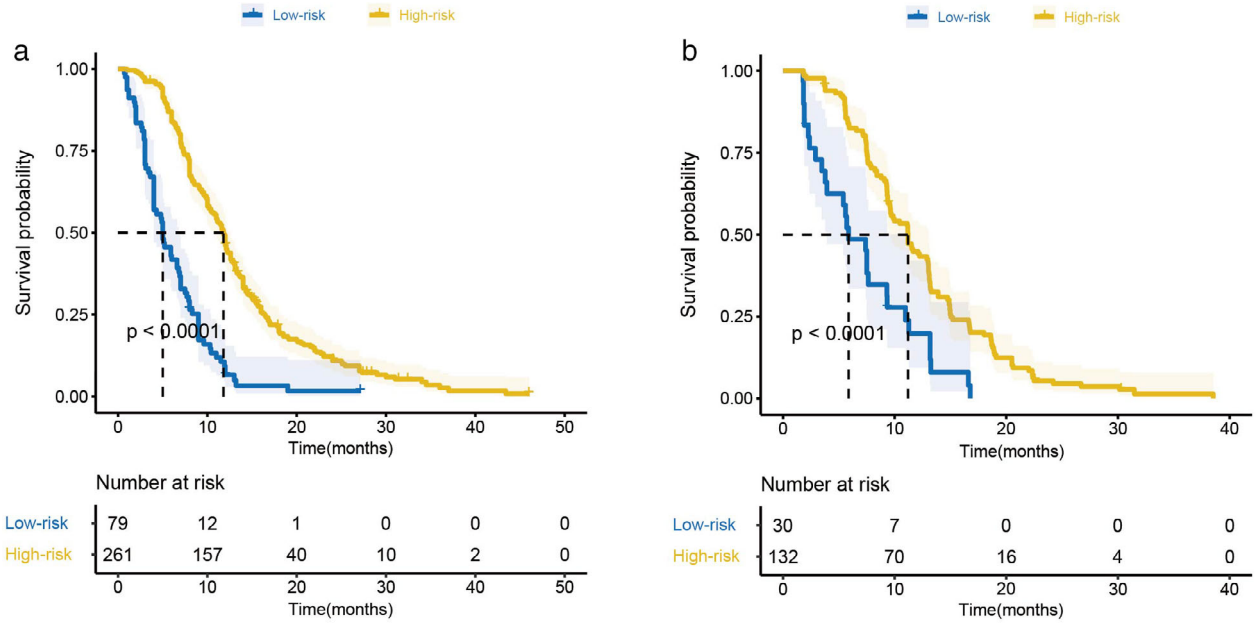

FIGURE 7 Kaplan–Meier curves of PFS for risk stratification. Kaplan–Meier curves of PFS for risk stratification in the training cohort (a) and the validation cohort (b)

ratio [HR], 3.552; 95% confidence interval [CI], 2.487–5.072; $p < 0.001$), EGFR mutation subtype (EGFR 21L858R:HR, 1.802; 95% CI, 1.427–2.275; $p < 0.001$), EGFR co-mutation (HR, 1.379; 95% CI, 1.021–1.863; $p = 0.036$), liver metastasis (HR, 1.720; 95% CI, 1.153–2.565; $p = 0.007$), and malignant pleural effusion (HR, 2.041; 95% CI, 1.514–2.752; $p < 0.001$) (Table 2; Figure 2).

Prognostic nomogram for PFS

The independent prognostic factors derived from the multivariate Cox analysis were integrated into nomogram models for PFS, including ECOG PS (0–1 or ≥2), EGFR mutation subtype (EGFR 19del or EGFR 21L858R), EGFR co-mutation, liver metastasis, and malignant pleural effusion (Figure 3). The value of each independent risk factor was given a score on the point axis. By adding the scores corresponding to the five variables of the patient and locating on the total point scale, the PFS probabilities of each patient could be obtained at the time points of 9-, 12-, 18-month PFS, and median PFS time.

For instance, patients with stage IV lung adenocarcinoma with EGFR19del mutation (0 point) had no malignant pleural effusion (0 point), liver metastasis (57.5 points), EGFR co-mutation (27 points), and performance status of ECOG 1 (0 point) at the first diagnosis, corresponds to the

sum of score of 72.5 in the nomogram, which indicates the 9-, 12-, 18-month PFS, and median PFS time of 47%, 28%, 7%, and 8.8 m, respectively.

Validation and performance of the nomogram

The C-indexes of the nomogram were 0.694 (95% CI, 0.663–0.725) for the training set and 0.653 (95% CI, 0.610–0.696) for the validation sets, respectively. The calibration plots for the probability of survival at 9-, 12-, and 18-month displayed an optimal agreement between the nomogram prediction and actual results (Figure 4). The above C-indexes correspond to the area under curve (AUC) value in the ROC curve analysis were 0.773, 0.770, and 0.712 in the training cohort and 0.707, 0.701, and 0.615 at 9-, 12-, and 18-month in the external validation cohort, respectively (Figure 5). According to the DCA, the net benefit rate was higher than EGFR mutation subtype as shown in DCA (Figure 6).

We calculated the best cut-off values of nomogram total scores, and divided the patients into low-risk and high-risk groups. In the training and validation cohort, the low-risk group had significantly better PFS than the high-risk group (Figure 7) ($p < 0.001$). The Kaplan–Meier curve of the PFS stratified according to prognosis groups showed good discrimination between the three prognosis groups, which suggested risk stratification can relatively accurately reflect the PFS situation in patients.

DISCUSSION

Despite the dramatic progress in diagnosis and treatment, the prognosis of advanced lung adenocarcinoma is still unsatisfactory and variable prognosis because of its heterogeneity. It has been demonstrated that individual NSCLC patients with oncogenic drivers who receive a matched targeted agent exhibit long-term survival. In addition, considering that a variety of high-risk factors other than the type of gene mutation affect the prognosis of stage IV lung adenocarcinoma, it is imprecise for clinicians to predict the survival using gene type. A valid prediction tool to identify advanced lung adenocarcinoma patients with promising prognostic factors can help clinicians make appropriate clinical decisions. However, it remains an unresolved challenge for physicians to stratify and predict the prognosis of advanced EGFR-sensitive mutant lung adenocarcinoma. Hitherto, only limited studies have reported that models were used to predict the PFS. Ng et al.[17] developed a robust nomogram-based risk score to predict OS in patients with EGFR mutant NSCLC, but did not accurately reflect the efficacy of first-line EGFR-TKIs treatment, because of the imbalance in access and availability of subsequent treatment options—known to be an important confounding variable for OS. Keam et al.[13] established nomogram to predict clinical outcomes in NSCLC, including patients in all lines of treatment, which might be affected by ECOG PS. In our study, we have established a prognostic model based on widely available baseline clinical features and molecular subclassification to predict the PFS of EGFR-sensitizing mutation, advanced lung adenocarcinoma patients treated with EGFR-TKIs. Our results show that the calibration of the nomogram reached moderate agreement in the training cohort and the external validation cohort. Although the C-indexes of the training cohort (0.694) and external validation cohort (0.653) were not high enough, the magnitudes of the discrimination ability of our nomogram were similar to those reported in previous studies.[13] We consider that sample size is one of the main contributors.

In our study, we identified five independent risk factors, including EGFR mutation status, EGFR co-mutation, ECOG PS, liver metastasis, and malignant pleural effusion, through a univariate analysis and multivariate analysis. Our study evaluated that EGFR mutation subtype is a reliable and independent predictor of the PFS, which was consistent with the previous studies.[18] More and more evidence showed the 19del mutation may be a more efficient clinical marker for predicting the response of patients with NSCLC to EGFR TKIs, and patients with EGFR 19del mutation have both a longer PFS and OS.[19–20] The potential distinct mechanisms are found from several dimensions including molecular structures, biological behaviors, resistance mechanisms, and tumor mutation burdens.[21–25] We divided these patients into two categories based on the co-mutation status, namely: (1) without co-mutation, the group that harbored EGFR-sensitizing mutations only; (2) with co-mutation, the group who carried EGFR-sensitizing mutations and tumor suppressor gene mutations (including TP53, RB1, and PTEN mutation) or any other driver mutation (including MET amplifications, ERBB2 amplifications, KRAS mutation and amplifications, BRAF amplifications, RET fusion). We found that the significant difference was observed in survival between the two subgroups. Moreover, the ECOG performance status was an independent factor affecting PFS and such population might experience more toxicity and require dose reduction.[26–27]

More than 40% of NSCLC patients present with distant metastasis at initial diagnosis. In this study, the most frequent sites of metastases are the bone, brain, malignant pleural effusion, and liver, which agreed with previous studies. It has been previously reported that liver metastasis was an independent unfavorable prognostic factor.[28] Whether receiving EGFR-TKIs or immunotherapy, patients with liver metastasis had poor survival outcomes.[29–30] Our results indicate that liver metastasis is a prognostic factor of PFS in both univariate and multivariate analysis. Yang et al.[31] evaluated the response rates to EGFR-TKIs in patients who had lung adenocarcinoma and cytology-positive malignant pleural effusion. In line with our data, the authors observed that pleural involvement as composite variable together with malignant pleural effusion both combined were associated with poor outcomes, which could be explained by the fact that pleural cavity is a natural permeable barrier that can

limit the penetration of cancer therapies.[32] With regard to the influence of bone metastasis on survival, most attention has been given to skeletal-related events (SREs), which impair quality of life and are understood to affect survival directly or indirectly.[33] In the present study, we did not observe specific effect of bone metastasis on PFS, which may indicate that EGFR-TKIs are effective and well tolerated in responders. Brain metastasis is one of the important factors affecting the life and quality of life of patients, with an average natural survival time of about 1–2 months.[34] In our study, patients without brain metastasis had improved PFS significantly, but not statistical difference ($p = 0.715$). This finding is consistent with those of previous reports showing both systemic and brain efficacy of EFGR-TKIs in patients with EFGR mutation NSCLC and brain metastases.[9,35–37]

We developed and validated a nomogram to predict the PFS of advanced lung adenocarcinoma patients treated with EGFR-TKIs, which based on the five independent risk factors. The calibration curves of the nomogram showed good consistency between the nomogram predictions and the actual observations. The risk factors we included were clinical variables at the initial diagnosis, and did not include variables related to or appearing in the treatment process, because we are looking for an effective diagnostic tool to provide personalized information about survival probability and make treatment-related decisions for patients and their oncologists. DCA shows that this prediction model can offer more net benefits than EGFR mutation subtype. This finding confirms the important role of risk-scores in the prognosis of NSCLC. We further constructed a risk stratification nomogram through ROC curve analysis, which can accurately evaluate the risk of patients with poor prognosis. Encouragingly, the low-risk group exhibited significantly better PFS than the high-risk group. Low-risk patients with liver metastasis identified by this prediction model may benefit from active local treatment of liver metastasis. As for advanced patients with high-risk score, treatment remained challenging. Zhao et al.[11] reported that combination therapy was beneficial for patients with EGFR L858R mutation, especially when combining EGFR-TKIs with antiangiogenic drugs. Therefore, based on the high-risk population identified by the model, we recommend the choice of combination therapy, but it should not excessively affect the quality of life.

There were several limitations of the current study. First, this study was restricted by the data collection of retrospective studies, which may lead to an unavoidable bias. Patient characteristic data were limited according to the retrospective medical records, making it difficult to collect more information, including histological grade, TN classification and so on. Second, osimertinib was approved by the National Medical Products Administration of China as the first-line treatment for patients with EGFR 19del/EGFR 21L858R mutation at September 2019 and the high cost of third-generation EGFR TKIs in the People's Republic of China; therefore, this study did not include sufficient data on osimertinib treatment. We need a different population from another center to externally validate this prediction model. Finally, the cohort is from a single-center study with small sample size. We should expand the sample size to explore the value of EGFR-TKIs choice in prognostic models. This will help predict progression free survival models with different EGFR TKIs in clinical practice. In the future, we are supposed to design a prospective trial to further validate the model, expand the sample size verification through other research centers, and include new prognostic variables to improve the nomogram.

In conclusion, we used baseline clinicopathological variables to develop and validate nomograms for prediction of individual survival in patients with EGFR mutation positive, advanced NSCLC treated with first-line EGFR-TKIs. The nomogram can optimize risk stratification management and comprehensively consider the prognostic risk factors of patients to adjust the treatment strategy more reasonably. Nevertheless, prospective cohort and longer-term follow-up studies are urgently needed to verify and extend the findings of our study.

ACKNOWLEDGMENTS

This work was supported by National key research and development project (2019YFC1315700); NSFC key program (81630071); NSFC general program (81871889, 81972905); Aiyou foundation (KY201701); Beijing Hope Run Special Fund of Cancer Foundation of China (LC2020B09 to J.X.); the Special Research Fund for Central Universities, Peking Union Medical College (3332021029 to J.X.).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Xinyang Du https://orcid.org/0000-0002-1594-7788
Jianchun Daun https://orcid.org/0000-0003-1479-2304
Yixiang Zhu https://orcid.org/0000-0003-2781-0962
Jie Wang https://orcid.org/0000-0002-5602-0487

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Du X, Bai H, Wang Z, Daun J, Liu Z, Xu J, et al. Establishment of prognostic nomograms for predicting the progression free survival of EGFR-sensitizing mutation, advanced lung cancer patients treated with EGFR-TKIs. Thorac Cancer. 2022;13:1289–98. https://doi.org/10.1111/1759-7714.14380