

# Bilirubin Can Be Used as a Prognostic Factor for Lung Adenocarcinoma Patients with EGFR Mutations

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**Background and Objectives:** Non-small cell lung cancer (NSCLC) patients with an epidermal growth factor receptor (*EGFR*) mutation demonstrate only a median progression-free survival (PFS) of 8 to 10 months and undergo EGFR tyrosine kinase inhibitors (EGFR-TKIs) therapy. For decades, bilirubin has been reported to be associated with the onset and prognosis of lung cancer as a prooxidant. This study aimed to investigate the prediction of pretreatment circulating bilirubin for PFS in lung adenocarcinoma (LAC) patients who underwent EGFR-TKIs targeted therapy.

**Patients and Methods:** LAC cases diagnosed and undergone EGFR-TKIs targeted therapy at The First Affiliated Hospital of Zhengzhou University between 2013 and 2015 were retrospectively reviewed. A total of 180 patients were studied according to inclusion and exclusion criteria. Follow-up data were collected for all patients until the disease progressed.

**Results:** Univariate analysis showed that the levels of pretreatment total bilirubin (TBIL), indirect bilirubin (IBIL) and direct bilirubin (DBIL) were related to PFS (all  $p < 0.05$ ). Considering the close relationship among the three factors, we combined TBIL, IBIL and DBIL into one total factor, which is called bilirubin. Kaplan–Meier survival curves and Log rank tests indicated that patients with lower bilirubin levels had a shorter median PFS than those with higher bilirubin levels (8 vs. 15 months;  $p = 0.002$ ). Multivariate analysis demonstrated that pretreatment bilirubin is an independent prognostic factor (HR=0.454, CI: 0.267–0.773,  $p = 0.004$ ).

**Conclusion:** This study confirms that bilirubin can predict the prognosis of LAC patients who had undergone EGFR-TKIs targeted therapy.

**Keywords:** bilirubin, lung adenocarcinoma, EGFR-TKIs, progression-free survival, prognosis

## Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, resulting in more than 1.5 million deaths every year.<sup>1,2</sup> Approximately 85% of all cases of lung cancer are characterised as non-small cell lung cancer (NSCLC), and lung adenocarcinoma (LAC) is the most common subtype of NSCLC.<sup>3,4</sup> Many lung cancers are advanced at the initial diagnosis, and recent advances in chemotherapy and targeted therapy have provided new treatment options for this disease. Specifically, NSCLC patients with activating epidermal growth factor receptor (*EGFR*) mutations are sensitive to small-molecule EGFR tyrosine kinase inhibitors (EGFR-TKIs).<sup>5,6</sup> These drugs have been recommended as the first-line regimen with dramatic tumour

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regression and progression-free survival (PFS) advantages compared with chemotherapy for patients in the advanced stages of lung cancer.<sup>7–10</sup>

However, most patients with NSCLC have acquired resistance to TKIs.<sup>11</sup> There is increasing evidence that several molecular biomarkers, such as *EGFR* mutations,<sup>12</sup> *EGFR* gene copy numbers,<sup>13</sup> and *K-ras* gene mutations,<sup>14</sup> are related to the prognosis of EGFR-TKIs targeted therapy. In general, these molecular biomarkers cannot be found in tissue samples until resistance has developed. Therefore, it is impossible to predict the prognosis in advance to consider intervention measures in a timely manner. Biological, clinical, and pathological factors, such as sex, smoking status, and race, are simple to obtain and can predict prognosis.<sup>5,15</sup> Therefore, we speculated whether simple and promising clinical factors could precisely predict the prognosis of NSCLC patients receiving EGFR-TKIs targeted therapy.

Many laboratory markers, such as c-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR) and monocyte counts, have been extensively discovered to play a significant role in influencing the prognosis of various types of tumours.<sup>16–20</sup> Haematological indicators from routine testing are not only economical but also readily available for repeated testing. In this study, we investigated the prognostic value of several laboratory parameters for patients with LAC who received EGFR-TKIs targeted therapy.

## Patients and Methods

### Patients

We conducted a retrospective analysis of patients diagnosed with LAC who had undergone EGFR-TKIs targeted therapy at The First Affiliated Hospital of Zhengzhou University between January 2013 and December 2015. All the patients met the following criteria: pathological confirmation of LAC, advanced tumour or recurrence (had surgery or chemoradiotherapy at least 6 months prior); *EGFR* mutation-positive and received EGFR-TKIs targeted therapy; at least one assessable lesion; completed clinical information; provided imaging examination and laboratory data. Patients with incomplete follow-up data, brain metastases, liver metastases or a predicted survival of less than three months were excluded. The research was supported by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University. We obtained consent and signed informed consent from the study participants before the study began. All the study participants agreed to the publication of this paper.

## Data Collection

The detailed clinical characteristics, including gender, age, the drug types of EGFR-TKIs, state of treatment (initial treatment or recurrence), laboratory variables, and imaging materials, were obtained. Disease stage was based on the 8th edition of the TNM classification of malignant tumours.<sup>21</sup> Blood samples were taken before treatment with EGFR-TKIs. Based on this, five haematology indexes of laboratory variables, including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), were extracted retrospectively from the medical records. Hematological indexes were divided into several groups based on quartile values, and then a cut-off point with the best significance in survival analysis was selected. At last, patients were divided into two groups with levels over and under the value. Patient progression outcomes were assessed using PFS, the period from the date of treatment to relapse or progression. Based on the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) guidelines,<sup>22,23</sup> the response was assessed by computed tomography (CT) once every two months or a CT scan of the patients after discomfort.

## Statistical Analysis

All statistical analyses were performed using SPSS version 17.0 software (SPSS, Inc., Chicago, Ill). Continuous variables were described using medians (range) or mean  $\pm$  SD, and categorical variables were given as absolute numbers (percentage values). Chi-squared test was used for comparative analysis of categorical variables, and Student's *t*-test was used for continuous variables. The cumulative survival curve and median PFS time were estimated by the Kaplan–Meier method. Differences between survival curves were tested for statistical significance using the two-tailed Log rank test. Multivariate prognostic analyses were performed for PFS using the Cox proportional hazards model. A two-tailed  $p < 0.05$  was considered to indicate a statistically significant difference.

## Results

### Patient Characteristics

Finally, 180 patients were recruited into the study according to the inclusion and exclusion criteria. In total, 69 patients (38.3%) were men and 111 patients (61.7%) were women. The median age at the time of therapy was 59 years (range: 30–85 years). Among them, 149 patients were treated with oral gefitinib, and 31 were treated with oral erlotinib. The

**Table 1** Baseline Clinicopathological Characteristics of Patients

Characteristics	Total (N = 180)
Age (median, range), years	59 (30 to 85)
Gender (Male/Female)	69/111
State of treatment (initial/recurrence)	138/42
Drugs (Gefinitib/erlotinib)	149/31
ALT (mean ± SD), U/L	23.750±20.212
AST (mean ± SD), U/L	23.360±13.202
TBIL (mean ± SD), μmol/L	9.410±5.004
DBIL (mean ± SD), μmol/L	4.030±2.136
IBIL (mean ± SD), μmol/L	5.380±3.180

**Abbreviations:** SD, standard deviation; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; IBIL, indirect bilirubin; DBIL, direct bilirubin.

baseline clinicopathological characteristics and information of these patients are summarised in Table 1.

## Survival Analysis

In this study, the median duration of follow-up for the PFS time was 7.0 months (range, 0.5 to 51). The median PFS was 14.0 months. At the time of the data cut-off, an event of RECIST-defined progression had occurred in 78 patients (43.3%), and the remaining 102 (56.7%) manifested as disease stabilisation or remission.

Univariate analysis was performed to determine the clinicopathologic characteristics that had a relationship with PFS. The results suggested that TBIL ( $p=0.003$ ), IBIL ( $p=0.008$ ) and DBIL ( $p=0.027$ ) were correlated with PFS. Nevertheless, age, gender, EGFR-TKIs drugs, state of treatment, ALT and AST were not statistically significant in predicting PFS ( $p>0.05$ ) (Table 2). The Log rank test and Kaplan–Meier survival curves indicated that patients with lower levels of TBIL<6.2 μmol/L, IBIL<3.2 μmol/L, and DBIL<3.55 μmol/L had shorter median survival times than those with higher levels (Figure 1). Considering the interaction of the three kinds of bilirubin in vivo, we analysed their correlation, and the results showed that the three kinds of bilirubin were linearly correlated (Figure 2). Patients with lower levels of TBIL, IBIL, and DBIL were grouped into one group as the lower group, and the rest were the higher group. We incorporated bilirubin into the Log rank test and found that patients in the lower group had a worse prognosis than patients in the higher group (8 vs. 15 months;  $p=0.002$ ), as shown in Figure 3. The results of multivariate analysis among clinical characteristics and laboratory variables showed that bilirubin ( $p=0.004$ ) was an independent prognostic factor to predict PFS (Table 3). Our results revealed that bilirubin is an independent prognostic factor for PFS.

**Table 2** Log Rank Test of Significant Indicators in Lung Adenocarcinoma Patients

Characteristics	Median PFS. Months (95% CI)	Chi-Square	p-value
Age, years			
<65	11 (6.319–15.681)	0.422	0.516
≥65	15 (11.108–18.892)		
Gender			
Male	16 (10.491–21.509)	0.035	0.851
Female	12 (8.230–15.770)		
State of treatment			
Initial	15 (10.945–18.245)	1.218	0.270
Recurrence	12 (8.154–15.846)		
Drugs			
Gefinitib	12 (8.274–15.726)	0.091	0.762
Erlotinib	11 (0.199–21.801)		
TBIL, μmol/L			
<6.2	8 (5.650–10.350)	8.713	0.003
≥6.2	15 (10.570–19.440)		
IBIL, μmol/L			
<3.2	8 (6.400–9.600)	7.005	0.008
≥3.2	15 (11.300–18.700)		
DBIL, μmol/L			
<3.55	10 (7.000–13.000)	4.893	0.027
≥3.55	16 (10.930–21.070)		

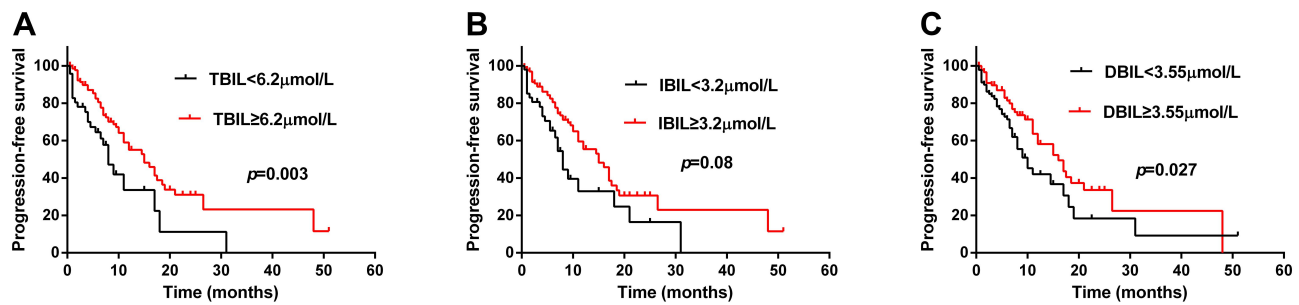
**Abbreviations:** PFS, progression-free survival; CI, confidence interval; TBIL, total bilirubin; IBIL, indirect bilirubin; DBIL, direct bilirubin.

## Association Between Bilirubin and Clinicopathologic Variables

We analyzed the relationship between bilirubin and ALT, AST and other clinical features, to exclude the influence of confounders. *T*-test of students showed that ALT and AST were not associated with bilirubin, and the difference was not statistically significant ( $p=0.86$ ,  $p=0.952$ , respectively). The chi-squared test results demonstrated that the age, gender, state of treatment, drugs were not associated with bilirubin ( $p>0.05$ ) (Table 4).

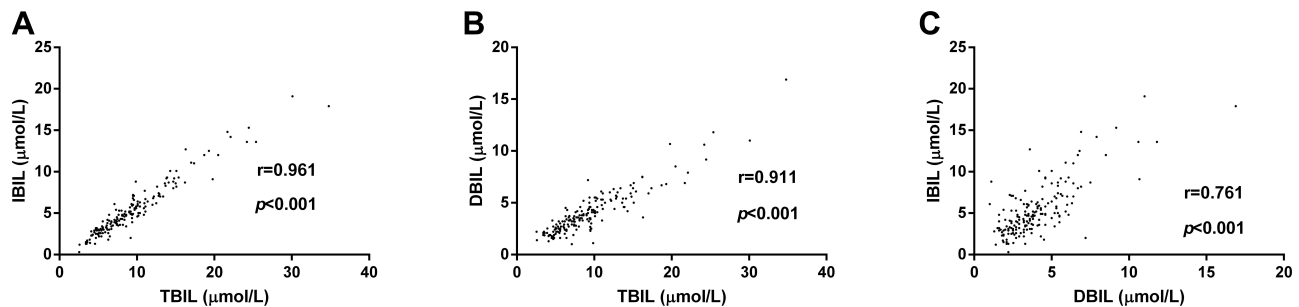
## Discussion

In recent years, bilirubin has been reported to be associated with the prognosis of cancers. Several recent studies have shown that slightly higher bilirubin levels appear to be beneficial for cancer patients. The higher is the total bilirubin level, the better is the prognosis of pancreatic cancer,<sup>24</sup> breast cancer<sup>25</sup> and lung cancer.<sup>26</sup> In our study,



**Figure 1** Significant differences were found in different levels of TBIL, IBIL and DBIL from the Kaplan–Meier survival curve. (A–C) Elevated pretreatment TBIL, IBIL and DBIL were significantly associated with better progression-free survival.

**Abbreviations:** TBIL, total bilirubin; IBIL, indirect bilirubin; DBIL, direct bilirubin.



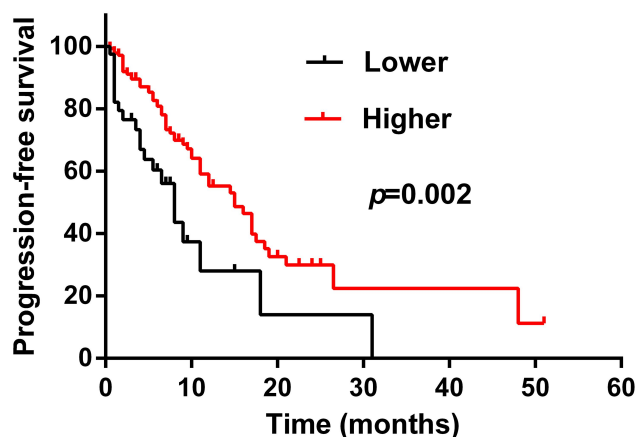
**Figure 2** Scatterplot of the relationship between TBIL, IBIL and DBIL. (A, B) TBIL is linearly dependent with IBIL and DBIL ( $r=0.911$ ;  $r=0.961$ , respectively); (C) The linear relation between DBIL and IBIL is not so obvious, but still shows a linear correlation ( $r=0.761$ ;  $p<0.001$ ).

**Abbreviation:**  $r$ , regression coefficient.

patients with higher levels of  $\text{TBIL} \geq 6.2 \mu\text{mol/L}$ ,  $\text{IBIL} \geq 3.2 \mu\text{mol/L}$ , and  $\text{DBIL} \geq 3.55 \mu\text{mol/L}$  had longer median survival times than those with lower levels. At the same time, the range of total bilirubin in the data we collected was 2.55–34.8  $\mu\text{mol/L}$ , with only three patients with abnormal levels ( $\geq 25 \mu\text{mol/L}$ ): 34.8  $\mu\text{mol/L}$ , 30.1  $\mu\text{mol/L}$  and 25.4  $\mu\text{mol/L}$ . Therefore, we conclude that a higher level of

pretreatment bilirubin within the normal range may predict a better prognosis in LAC patients who received EGFR-TKIs.

Bilirubin is the main end product of heme degradation, which can cause irreversible damage to the brain and nervous system. However, bilirubin also shows important cellular protective effects, with antioxidant<sup>27</sup> and anti-inflammatory antioxidant capacity.<sup>28</sup> Notably, bilirubin also induces apoptosis and anti-proliferation and inhibits the growth of various tumour cells. The mechanisms by which bilirubin inhibits cell growth include the induction of oxidative stress and mitochondrial depolarisation.<sup>29,30</sup>



**Figure 3** The Kaplan–Meier survival curve of bilirubin factor. Higher bilirubin factor was significantly associated with better progression-free survival.

**Table 3** Multivariate Survival Analysis in Relation to PFS in Lung Adenocarcinoma Patients

Characteristics	HR	95% CI	p-value
Bilirubin, lower/higher	0.454	0.267–0.773	0.004
Gender, Male/Female	0.989	0.621–1.575	0.963
Age, <65/≥65, years	0.952	0.583–1.554	0.844
State of treatment (initial/recurrence)	1.119	0.922–1.358	0.256
Drugs, Gefinitib/Erlotinib	1.188	0.661–2.135	0.565

**Abbreviations:** HR, hazard ratio; CI, confidence interval.

**Table 4** Correlation Between Total Bilirubin and Clinical Characteristics

Variables	Lower (n=40)	Higher (n=140)	p-value
Age, years			
<65	31 (77.5%)	94(67.1%)	0.144
≥65	9 (22.5%)	46(32.9%)	
Gender			
Male	12 (30%)	57(40.7%)	0.219
Female	28 (70%)	83(59.3%)	
State of treatment			
Initial	11 (27.5%)	31 (22.1%)	0.480
Recurrence	29 (72.5%)	109 (77.9%)	
Drugs			
Gefitinib	36 (85%)	113(80.7%)	0.170
Erlotinib	6 (15%)	27 (19.3%)	

**Abbreviation:** n, the number of patients in each group.

In many studies, bilirubin is associated with lower tumorigenesis<sup>31–33</sup> and cancer mortality.<sup>34</sup> Those with elevated bilirubin had a longer overall survival than those with normal bilirubin. Some studies have shown that serum bilirubin is a positive prognostic factor in lung cancer with strong antioxidant and antitumour effects<sup>26,35</sup> which is consistent with ours. However, the relationship between bilirubin and lung cancer survival remains controversial. In Yanwei Zhang et al's study, direct bilirubin was identified as a prognostic risk factor for advanced NSCLC patients with *EGFR* mutations.<sup>36</sup> Regarding the existence of controversy, we suspect that this difference may be due to different patient characteristics.

In our study, higher levels of bilirubin predicted a good prognosis in patients with advanced NSCLC with *EGFR* mutations. To our best knowledge, this is the first report showing the beneficial prognostic value of bilirubin in LAC patients who received *EGFR*-TKIs targeted therapy. Our research demonstrated that bilirubin (HR=0.454, CI: 0.267–0.773,  $p=0.004$ ) is an independent prognostic factor for PFS, and the prognosis is poor in the lower group ( $p=0.002$ ). When the data were collected in this study, we excluded patients with liver metastases to ensure the effect of liver function on the results. The correlation analysis between bilirubin and patient age, gender, state of treatment, drugs, ALT, AST showed no relationship between them ( $p>0.05$ ); thus, we excluded their effect on the patient's bilirubin. We hypothesise that total bilirubin may be a predictor of LAC patients receiving *EGFR*-TKIs targeted therapy based on antioxidant, anti-inflammatory and anti-proliferative effects.

This study is a retrospective study, which inevitably has some limitations. First, like other retrospective studies, we cannot completely rule out the impact of selection bias. Second, our study include is limited by its single-centre and retrospective design. Third, China constitutes the entirety of our population sample. Our results may not apply to other ethnic populations. However, the findings of this study may help to facilitate the understanding of the relationship between the tumour microenvironment and clinical factors. Additionally, larger and more detailed prospective studies are needed to further clarify these relationships.

## Conclusion

We have demonstrated that bilirubin is an independent predictor for NSCLC patients who are treated with *EGFR*-TKIs targeted therapy. Moreover, patients with higher pretreatment serum bilirubin levels have a longer PFS than those with lower pretreatment serum bilirubin levels. Further well-designed studies with more patients and longer follow-up times are warranted to confirm the prognostic value of bilirubin levels in NSCLC, considering other potential prognostic factors for NSCLC.

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## Author Contributions

Yimeng Geng and Yeling Mei are responsible for conception, study design, data analysis and interpretation, drafting the article. Ying Xi, Junlin Yu and Ke Meng are responsible for acquisition of data, data analysis and interpretation, and critically revised the article. Tengfei Zhang and Wang Ma are responsible for study execution and substantially revised the article. All authors have agreed on the journal to which the article will be submitted. All authors agreed to take responsibility and be accountable for the contents of the article, reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage, and agreed to take responsibility and be accountable for the contents of the article.

## Disclosure

The authors declare no conflicts of interest.

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