Medical Research
Volume 7, Issue 1, 2025, Page 28-36
https://doi.org/10.6913/mrhk.070105

Medical Research

A Study on the Relationship between EGFR Gene Mutations and the Clinical Characteristics and Tumor Markers in Patients with Non-Small Cell Lung Cancer

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Abstract

[Aims] This study aims to explore the relationship between epidermal growth factor receptor (EGFR) mutations and clinical characteristics, as well as serum tumor markers, in patients with non-small cell lung cancer (NSCLC), and to assess the implications of these findings. **[Methods]** The study included 105 NSCLC patients diagnosed at the Seventh Affiliated Hospital of Sun Yat-sen University between January 2020 and November 2024. Based on EGFR gene testing results, the patients were divided into two groups: the mutation group(63 patients) and the wild-type group (42 patients). The clinical characteristics of both groups were compared, and the associations between serum blood tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigen 125 [CA125], carbohydrate antigen 199 [CA199], squamous cell carcinoma antigen [SCCA]) and EGFR mutations were analyzed. **[Results]** In the mutation group , the proportion of females and non-smokers was significantly higher compared to the wild-type group ($P < 0.05$). Moreover, the mutation group exhibited a higher positive rate of CEA ($P < 0.05$) and a lower positive rate of SCCA ($P < 0.05$) compared to the wild-type group. Spearman correlation analysis revealed significant relationship between EGFR mutation status and patient gender, smoking history, CEA, and SCCA ($P < 0.05$). Multivariate logistic regression analysis identified smoking history, CEA, and SCCA as independent factors influencing EGFR mutations. **[Conclusion]** EGFR mutations are significantly associated with patient gender, smoking history, CEA, and SCCA in NSCLC. Clinical characteristics and monitoring of serum CEA and SCCA levels may provide valuable insights for predicting EGFR mutation status.

Keywords Epidermal growth factor receptor; Non-small-cell lung cancer; Clinical characteristics; Serum tumor markers; relationship

To Cite This Article Bohui ZHAN,et al. (2025). A Study on the Relationship between EGFR Gene Mutations and the Clinical Characteristics and Tumor Markers in Patients with Non-Small Cell Lung Cancer. *Medical Research*, 7(1), 28-36. https://doi.org/10.6913/mrhk.070105

Medical Research, ISSN 2664-0333 (print), ISSN 2664-0341 (online), DOI 10.6913/mrhk, a bimonthly, founded on 2018, Indexed by CNKI, Google Scholar, AIRITI, Scilit, CrossRef, Elsevier PlumX, etc., published by Creative Publishing Co., Limited. Email: wtocom@gmail.com, https://mrhk.cc, https://cpcl.hk.

1 Introduction

Lung cancer is the most common malignancy in our country and the leading cause of cancer-related deaths[1]. Among its various types, non-small cell lung cancer (NSCLC) accounts for 80% to 85% of cases, exhibiting the highest incidence and mortality rates among malignant tumors in clinical practice, and thus severely impacting patients' survival and overall well-being. Since most patients are diagnosed at an advanced stage, curative surgery is typically not an option[2]. Consequently, exploring effective treatment strategies is critical for improving patient outcomes.

In recent years, targeted therapies against the epidermal growth factor receptor (EGFR) have significantly improved treatment responses and prolonged survival in patients harboring specific EGFR mutations[3]. Furthermore, Asian NSCLC patients are more likely to carry EGFR mutations and tend to respond better to EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy[4].

However, the high cost of EGFR gene testing, along with factors such as the poor physical condition of many NSCLC patients and the limited availability of minimally invasive specimens, has contributed to a relatively low rate of genetic testing. In contrast, the detection of serum tumor markers is more accessible in clinical practice. These markers not only assist in diagnosis but also play an important role in guiding targeted therapy for NSCLC patients.

This study analyzed 105 NSCLC patients admitted to our institution between January 2020 and November 2024, aiming to present clinically relevant and reliable findings.

2 Materials and Methods

2.1 Study Design and Patient Cohort

This study included 63 patients with EGFR-mutant NSCLC who were admitted to the Seventh Affiliated Hospital of Sun Yat-sen University between January 2020 and November 2024 (mutation group), and 42 patients with EGFR wild-type NSCLC who served as the control group (wild-type group). The inclusion criteria were as follows: (1)a confirmed diagnosis of NSCLC based on pathology or cytology;(2) receipt of EGFR gene testing. The exclusion criteria were as follows: (1) presence of other malignancies; (2) liver or kidney dysfunction, autoimmune diseases, hematological disorders, or other significant comorbidities. In the mutation group, there were 27 male and 36 female patients, with a mean age of 61.22 ± 10.43 years; 8 patients had a history of smoking. Clinical staging revealed that 30 patients were in stages I II, and 33 were in stages III IV. In the wild-type group, there were 27 male and 15 female patients, with a mean age of 62.07 ± 10.89 years; 13 patients had a history of smoking. Clinical staging showed that 23 patients were in stages I II, and 19 were in stages III IV. This study was approved by the Ethics Committee of the Seventh Affiliated Hospital of Sun Yat-sen University.

2.2 Detection of EGFR Mutations

The amplification refractory mutation system (ARMS) method was used to detect common mutations in the EGFR gene. A Bio-Rad S1000 PCR amplifier was employed for quantitative fluorescence PCR. The reagent kit was provided by Burning Rock Medical Laboratory Co., Ltd., Guangzhou, China.

2.3 Detection of Tumor Markers

Serum tumor markers (STMs) were measured using a commercial chemiluminescence immunoassay kit (Abbott Laboratories, I2000, USA). Peripheral venous blood samples were collected from all participants before any anticancer treatment. Tumor marker values exceeding the normal reference range specified in the kit's instructions were considered positive.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS 23.0 software. Categorical variables were compared between groups using the chi-squared test or Fisher's exact test, while continuous variables were analyzed using the independent samples t-test. The relationship between various indicators and EGFR mutation status was assessed using Spearman's correlation coefficient. Variables potentially influencing EGFR mutations were included in a binary logistic regression model to evaluate the predictive value of each indicator. A P-value < 0.05 was considered statistically significant.

3 Results

3.1 Distribution of EGFR Gene Mutation Types

This study included 105 patients with NSCLC, among whom 63 were found to have EGFR mutations, yielding a mutation rate of 60%. Of these, 57 patients had single-site mutations, with exon 21 being the most common (29 cases), followed by exon 19 (25 cases).

Additionally, 6 patients exhibited double-site mutations, most of which involved exon 21 in combination with other exons (5 cases). The most frequent specific mutation was the exon 21 L858R mutation (28 cases), followed by the exon 19 deletion (19del) mutation (25 cases).

Further details are presented in Table 1.

3.2 Relationship Between EGFR Mutations and Clinical Characteristics in NSCLC Patients

Compared with the wild-type group, the mutation group had a significantly higher proportion of female patients and non-smokers ($P < 0.05$). However, no significant differences were observed between the two groups in terms of age, TNM stage, or the presence of distant organ and/or lymph node metastases ($P > 0.05$), as summarized in Table 2.

Table 1: Distribution of EGFR Gene Mutation Types

EGFR mutation variants	example number	The percentage of mutation cases (%)
Exon 19 (19del)	25	39.68%
Exon 21 (L858R)	28	44.44%
Exon 21 (L861Q)	1	1.59%
p.L858R and p.K757R	1	1.59%
p.L858R and p.T790M	1	1.59%
p.L858R and p.R776H	1	1.59%
p.L858R and p.E709K	1	1.59%
p.L858R and p.T263P	1	1.59%
Exon20(p.D770_N771insGD)	1	1.59%
Exon20(p.H773_V774insPHPH)	1	1.59%
Exon20(p.H773dup)	1	1.59%
p.S768I and p.V774M	1	1.59%

Table 2: The relationship between EGFR mutations and clinical characteristics in NSCLC patients.

Characteristics	EGFR（n=105）		t or χ^2 value	P value
	The mutation group	The wild-type group		
Age (years)	61.22±10.43	62.07±10.89	-0.402	0.689
≤60	26（41.3%）	19（45.2%）	0.162	0.687
＞60	37（58.7%）	23（54.8%）		
Gender				
Male	27（42.9%）	27（64.3%）	4.632	0.031
Female	36（57.1%）	15（35.7%）		
Smoking				
Yes	8（12.7%）	13（31.7%）	5.569	0.018
No	55（87.3%）	28（68.3%）		
TNM stage				
I～II	30（47.6%）	23（54.8%）	0.514	0.473
III～IV	33（52.4%）	19（45.2%）		
Distant organ and/or lymph node metastasis				
Yes	34（54.0%）	20（47.6%）	0.407	0.524
No	29（46.0%）	22（52.4%）		

3.3 Relationship Between EGFR Gene Mutations and Tumor Markers in NSCLC Patients

The positive rate of CEA in the EGFR mutation group was 49.21%, compared to 28.57% in the wild-type group. Chi-square analysis revealed a statistically significant difference between the two groups ($\chi^2 = 4.437$, $P < 0.05$).

Similarly, the positive rate of SCCA was significantly lower in the mutation group (1.61%) than in the wild-type group (19.05%), with the chi-square test also indicating statistical significance ($\chi^2 = 7.549$, $P < 0.05$), as shown in **Table 3.**

Table 3: The relationship between EGFR gene mutations and tumor markers in NSCLC patients.

Group	CEA positive	CA125 positive	CA199 positive	SCCA positive
The mutation group	31（49.21%）	20（35.09%）	6（10.34%）	1（1.61%）
The wild-type group	12（28.57%）	10（28.57%）	5（14.29%）	8（19..05%）
χ^2 value	4.437	0.419	0.057	7.549
P value	0.035	0.517	0.811	0.006

3.4 Analysis of the Correlation Between Clinical Indicators and EGFR Mutations in NSCLC Patients

Spearman correlation analysis revealed a positive association between EGFR mutation status and gender (r = 0.210, P = 0.032), indicating that EGFR mutations are more likely to occur in female patients. A significant negative correlation was observed with smoking history (r = -0.231, P = 0.018), suggesting a higher mutation rate among non-smokers.

In addition, EGFR mutation status showed a positive correlation with CEA levels (r= 0.206, P = 0.035), implying that patients with EGFR mutations tend to exhibit higher CEA positivity. Conversely, a negative correlation was identified with SCCA levels (r = -0.304, P = 0.002), indicating a lower SCCA positivity rate in the mutation group.

No statistically significant correlations were found between EGFR mutation status and other clinical indicators, as shown in Table 4.

Table 4: Analysis of the Correlation Between Clinical characteristics and EGFR Mutations in NSCLC Patients.

Indicators	Correlation coefficient(r)	P value
Age (years)	0.039	0.691
Gender	0.210	0.032
Smoking（Yes/No）	-0.231	0.018
TNM stage	0.070	0.478
Distant organ and/or lymph node metastasis（Yes/No）	0.062	0.528
CEA（Positive/Negative）	0.206	0.035
CA125（Positive/Negative）	0.067	0.523
CA199（Positive/Negative）	-0.059	0.573
SCCA（Positive/Negative）	-0.304	0.002

3.5 Multivariate Analysis Predicting EGFR Mutations in NSCLC Patients

A binary logistic regression analysis was performed using the statistically significant variables from univariate analysis as independent variables, and EGFR mutation status as the dependent variable. The results showed that the risk of EGFR mutation in smoking patients was 0.199 times that of non-smokers (OR = 0.199, 95% CI: 0.047 0.834).

Patients with positive serum CEA levels had a 6.376-fold increased risk of harboring EGFR mutations compared to those with negative CEA levels (OR = 6.376, 95% CI: 1.951 20.840).

Conversely, the risk of EGFR mutation in patients with positive serum SCCA levels was 0.077 times that of those with negative SCCA levels (OR = 0.077, 95% CI: 0.007 0.812).

All corresponding Wald test results were statistically significant ($P < 0.05$), indicating that smoking history, CEA, and SCCA are independent predictors of EGFR gene mutations, as summarized in Table 5.

Table 5: Binary logistic regression analysis of predictive factors for EGFR mutations.

Indicators	B	SE	Wald	P value	Exp(B)	95%CI
Gender	0.595	0.542	1.205	0.272	1.814	0.626-5.251
Smoking	-1.617	0.732	4.872	0.027	0.199	0.047-0.834
CEA	1.853	0.604	9.399	0.002	6.376	1.951-20.840
SCCA	-2.567	1.203	4.548	0.033	0.077	0.007-0.812

4 Discussion

4.1 The Significance of EGFR Mutations in NSCLC

Non-small cell lung cancer (NSCLC) is a highly heterogeneous malignancy, involving a range of molecular events and alterations in signaling pathways [4]. Among these, mutations in the epidermal growth factor receptor (EGFR) gene play a pivotal role in the initiation and progression of NSCLC [5]. These mutations are closely associated with the disease' s biological behavior and have a profound impact on the efficacy of targeted therapies.

With recent advances in molecular biology, the accurate identification of EGFR mutations has become essential in guiding individualized treatment strategies for NSCLC. Previous studies have demonstrated that EGFR mutations are strong predictors of response to EGFR tyrosine kinase inhibitors (EGFR-TKIs) [6]. Accordingly, the ability to predict EGFR mutation status holds significant clinical value for both diagnosis and therapeutic decision-making in NSCLC.

However, the widespread application of EGFR gene testing is often limited by high costs and complex technical requirements. Therefore, developing reliable and accessible approaches for predicting EGFR mutation status may improve the clinical utility of EGFR-TKI therapies and provide a more practical basis for prognostic evaluation in patients with NSCLC.

4.2 Clinical Characteristics Associated with EGFR Mutations

Previous studies have demonstrated that clinical characteristics such as gender and smoking status are significantly associated with EGFR mutation status. Specifically, female and non-smoking patients tend to have higher EGFR mutation rates and respond better to EGFR-TKI therapy.

In the present study, clinical data from 105 NSCLC patients revealed a higher mutation rate in female and non-smoking patients compared to their male and smoking counterparts, which is consistent with the findings reported by Mok et al. [7–9]. These results suggest that female gender

and non-smoking status are predictive factors for EGFR mutations in NSCLC, providing valuable information for guiding the selection of EGFR-TKI therapy [10].

4.3 CEA as a Predictor of EGFR Mutations

Tumor markers are substances produced and secreted by tumor cells, playing a crucial role in the diagnosis of malignancies, evaluation of treatment efficacy, and prediction of tumor recurrence. Carcinoembryonic antigen (CEA) is one of the earliest tumor markers used in the diagnosis of NSCLC and remains one of the most clinically valuable indicators for lung cancer assessment.

Serum CEA levels were significantly elevated in individuals with EGFR mutations compared to those with wild-type EGFR, as demonstrated by Feng LX et al. [11]. Similarly, a retrospective study by Wang et al. [12] reported that higher CEA levels were associated with an increased risk of EGFR mutations.

In the present study, patients with EGFR mutations showed a significantly higher CEA positivity rate than those with wild-type EGFR ($P < 0.05$). Logistic regression analysis further confirmed that patients with positive CEA had a 6.376-fold higher risk of harboring EGFR mutations compared to those with negative CEA (OR = 6.376, 95% CI: 1.951 20.840). These findings are consistent with the results of Wen et al. [13], who also identified CEA as an independent predictor of EGFR gene mutations.

The underlying mechanism may involve EGFR mutation-induced activation of downstream signaling pathways, which subsequently activate transcription factors involved in anti-apoptotic signaling and cell proliferation [14,15]. In NSCLC, EGFR mutations are often correlated with higher tumor aggressiveness and invasiveness. These biological changes can lead to increased tumor tissue turnover and enhanced release of tumor markers into the bloodstream.

Moreover, elevated CEA levels may contribute to tumor progression by promoting cancer cell adhesion, facilitating detachment from the extracellular matrix, and inhibiting apoptosis. CEA may thus function as an anti-apoptotic factor within the EGFR signaling cascade. Taken together, these findings suggest that patients with elevated serum CEA levels are more likely to carry EGFR mutations.

4.4 SCCA and Other Markers in EGFR Mutation Prediction

A study by Sufei Wang involving 1,089 NSCLC patients reported a correlation between negative expression of CA125, SCCA, and CA199 and the presence of EGFR mutations [12]. Although SCCA is traditionally associated with squamous cell carcinoma, it can also be expressed in certain adenocarcinomas [13,16].

In the present study, the proportion of SCCA-negative patients was significantly higher in the EGFR mutation group than in the wild-type group. Logistic regression analysis identified serum SCCA as an independent factor associated with EGFR mutations. Specifically, the likelihood of harboring EGFR mutations in patients with positive SCCA expression was only 0.077 times that of those with negative SCCA expression (OR = 0.077, 95% CI: 0.007 0.812).

These findings suggest that serum SCCA may serve as a potential negative predictor for EGFR mutation status. However, not all tumor markers showed a significant association with EGFR mutations. In this study, no significant correlations were observed between CA125, CA199, and EGFR mutation status.

Given the relatively limited sample size and variability in baseline characteristics, discrepancies with previous research may exist. To date, few clinical studies have systematically explored the relationship between pre-treatment serum tumor marker levels and EGFR mutations. Further large-scale investigations are warranted to validate these findings.

4.5 Integrated Marker-Based Prediction and Study Limitations

Logistic regression analysis suggests that, in non-smoking patients, elevated serum CEA levels combined with normal SCCA levels may indicate the presence of EGFR mutations. These findings underscore the importance of integrating patients' smoking history with serum tumor markers—particularly CEA and SCCA—to improve the prediction of EGFR mutation status in the diagnosis and management of NSCLC. This approach may offer significant clinical guidance, especially for patients who are unable to undergo genetic testing.

In conclusion, tumor markers such as CEA and SCCA can serve as valuable predictors of EGFR gene mutations. The combination of tumor marker analysis with clinical characteristics may enhance the accuracy of EGFR mutation prediction. Therefore, utilizing serum tumor markers and clinical features to infer EGFR mutation status holds substantial clinical relevance, particularly in settings where genetic testing is limited or unavailable, and can help optimize the application of EGFR-TKI therapy.

Nonetheless, this study is subject to certain limitations, primarily due to its relatively small sample size. Future research should aim to validate these findings by expanding the sample size and conducting more comprehensive, multicenter investigations.

Article History

Received: January 10, 2024 **Accepted:** January 28, 2025 **Published:** March 31, 2025

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