

Frequency of EGFR Mutations and Associated Clinical Factors in Thai Patients with Non-small Cell Lung Cancer (NSCLC)

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ABSTRACT

OBJECTIVE Understanding clinical factors related to epidermal growth factor receptor (EGFR) mutation in lung cancer patients is imperative for effective treatment planning. It is also crucial to recognize ethnic differences. Hence, studying the prevalence and types of EGFR mutations in Thai patients with non-small cell lung cancer (NSCLC) is essential. Investigating clinical factors influencing EGFR mutation detection remains critical.

METHODS Etiognostic research with a retrospective observational cohort design collected clinical data from NSCLC patients undergoing EGFR molecular testing using real-time PCR from November 1, 2017 to September 30, 2022. The relationship between smoking as well as other clinical factors of interest and the detection of EGFR mutation through regression were analyzed.

RESULTS The EGFR mutation rate was 46.55%, with 108 cases detected out of 232 patients. EGFR mutation was detected in 63.41% of the never smoking group. Exon 19 deletion (51.85%) and exon 21 L858R mutation (36.11%) were the predominant types. Univariable regression analysis identified factors correlated with EGFR mutation detection, including female gender, non-smoker status, adenocarcinoma lung cancer type, and bone metastasis. A statistically significant reduction in EGFR mutation detection was observed in patients with squamous cell carcinoma lung cancer. Multivariable regression analysis confirmed non-smoker and adenocarcinoma lung cancer type as significant independent predictors of EGFR mutation detection (adjusted OR 2.84, 95%CI 1.20-6.74, $p = 0.018$) (adjusted OR 14.39, 95%CI 1.77-116.84, $p = 0.013$), respectively. The survival analysis results showed significant survival differences between stage 4 NSCLC patients with EGFR mutations and EGFR wild-type (median overall survival: 22.98 months vs 8.72 months, median survival time difference: 12.60 months, $p < 0.001$).

CONCLUSIONS Adenocarcinoma and non-smoker status represent significant factors associated with EGFR mutation. Nonetheless, performing an EGFR test before initiating treatment remains crucial as it enhances treatment precision and specificity.

KEYWORDS epidermal growth factor receptor, EGFR, non-small cell lung cancer, NSCLC, Thai, clinical factors

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INTRODUCTION

Genetic alterations in the epidermal growth factor receptor (EGFR) gene are widely acknowledged to have a significant role in non-small cell lung cancer (NSCLC) pathogenesis (1, 2). EGFR plays a critical role in a multitude of cellular processes, encompassing cell proliferation, differentiation, motility, and survival. Binding of epidermal growth factor (EGF) to EGFR induces receptor dimerization, autophosphorylation, and subsequent activation, initiating a myriad of molecular pathways that culminate in cell activation. Normally, EGFR activation ceases upon exhaustion of its ligands, including EGF, transforming growth factor alpha (TGF- α) and various other growth factors. EGFR gene mutations can overactivate EGFR signaling pathways, leading to uncontrolled cellular proliferation and tumor development (3). International studies have reported varying frequencies of EGFR mutations among Asian and Western populations. Western populations have a 10% prevalence rate of EGFR mutation, while in Asian populations, the prevalence ranges between 50–60% (4, 5). Understanding the mechanisms of EGFR gene alterations in NSCLC is crucial for developing precise therapeutic interventions and improving patient outcomes. In NSCLC with overexpressed EGFR, inhibition of receptor signaling, particularly with TKIs like gefitinib, erlotinib and osimertinib, is considered optimal for those with EGFR-activating mutations (6, 7).

Epidemiological data and clinical behaviors related to EGFR and lung cancer vary among ethnic groups (8, 9). In Thailand, a study was conducted on the frequency of detection of EGFR mutations in patients with NSCLC from formalin-fixed paraffin-embedded tissue using polymerase chain reaction–single strand conformational polymorphism (PCR–SSCP). It was found that EGFR mutations occurred in about 58% of the cases (10, 11). However, the data from that study has limitations due to the small sample size and because it does not include the clinical relationship dimension of the patients, especially clinical factors related to smoking, because the data was derived from pathological examination. This gap in information on the patient clinical profiles may have affected the interpretation of the EGFR mutation frequency. Moreover, factors related to lung cancer treatment, such as treatment efficacy and patient

outcomes, also need to be considered. These factors may vary depending on the presence or absence of EGFR mutations in practical clinical settings, highlighting further limitations in the study's findings.

The present study aims to investigate the prevalence of EGFR mutations in Thai patients with NSCLC, as well as the types of mutations detected and clinical factors that affect EGFR mutation detection.

METHODS

This is an etiognostic research study with a retrospective observational cohort design. It collected clinical factors data from patients with NSCLC stage 4 who received treatment at the Oncology Unit, Buddhasothorn Hospital and who underwent EGFR molecular testing using real-time PCR between November 1, 2017 and September 30, 2022.

Determination of whether the data conformed to a normal distribution was determined by conducting a Shapiro–Wilk test for independent categorical variables. Data from the test are displayed as counts and percentages. The data were analyzed and compared using either the Chi-square test or Fisher's exact test. The relationship between smoking and other clinical factors of interest and the detection of EGFR mutations was investigated using regression analysis. The survival analysis was conducted using the Kaplan–Meier curve, and the mean differences in survival between the EGFR mutation group and the wild-type group were tested using Laplace regression.

The objective of the research is to study both the frequency of EGFR mutation in patients with NSCLC and the types of mutations in Thai patients. Additionally, the research aims to investigate the relationship between smoking and types of NSCLC with the detection of EGFR mutations, as well as to explore the correlation between detection of EGFR mutations and clinical factors.

The study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital (number BSH-IRB 010/2566).

RESULTS

Data are for 392 patients with NSCLC stage 4 treated at Buddhasothorn Hospital between November 1, 2017 and September 30, 2022. A total

of 160 cases were excluded due to insufficient data because the EGFR molecular test had not been performed, and 232 cases were analyzed in the study. The flowchart for data selection is shown in Figure 1. Among the patients, 121 (52.16%) were male and 111 (47.84%) were female. The average age of patients of both genders combined was 63.51 years, with a standard deviation of ± 0.70 . Concerning NSCLC cell types, the majority of cases were adenocarcinoma, accounting for 90.52%. Squamous cell carcinoma followed with 8.19%, and other cell types with 1.29%. The distribution of initial metastatic sites demonstrated variability. Specifically, there were 26 cases (11.21%) of brain metastasis, 187 cases (80.60%) of lung-to-lung metastasis, 118 cases (50.86%) of pleural metastasis, 38 cases (16.38%) of liver metastasis, and 76 cases (32.76%) of bone metastasis (Table 1).

Analysis of EGFR mutation frequencies determined that there were 124 cases (53.45%) of the EGFR wild type and 108 cases (46.55%) of mutations. EGFR mutations detected were primary mutations before the start of treatment. The types of EGFR mutations identified included Exon 19, accounting for 51.85%, and Exon 21 L858R, which constituted 36.11%. Additionally, we observed an uncommon EGFR mutation comprising Exon 18 G719X and Exon 21L861Q to be present in 4.63% of cases. Furthermore, a dual EGFR mutation involving both Exon 19 deletion and Exon 21L858R

was identified in 2.78% of cases. Other mutations, such as EGFR Exon 20 insertions, were present in 1.85% of cases. Additionally, a common EGFR mutation plus the primary T790M mutation was observed in 1.85% of cases, and a primary EGFR T790M mutation was found in 0.93% of cases (Table 2).

After categorizing the mutations into the EGFR wild type and EGFR groups, we investigated the correlation with clinical factors. Analysis

Table 1. Baseline characteristics of non-small cell lung cancer (NSCLC)

	Mean age ($\pm$ SD) / 95%CI
Overall patients	63.51 ($\pm$ 0.70) / 62.14–64.89
Male	64.44 ($\pm$ 0.97) / 62.51–66.37
Female	62.50 ($\pm$ 0.99) / 60.53–64.47
	Number (%)
Smoking	
Former/current smokers	109 (46.98)
Never-smokers	123 (53.02)
Type of NSCLC	
Adenocarcinoma	210 (90.52)
Squamous cell carcinoma	19 (8.19)
Other type	3 (1.29)
Initial metastatic site	
Brain metastasis	26 (11.21)
Lung to lung metastasis	187 (80.60)
Pleural metastasis	118 (50.86)
Liver metastasis	38 (16.38)
Bone metastasis	76 (32.76)

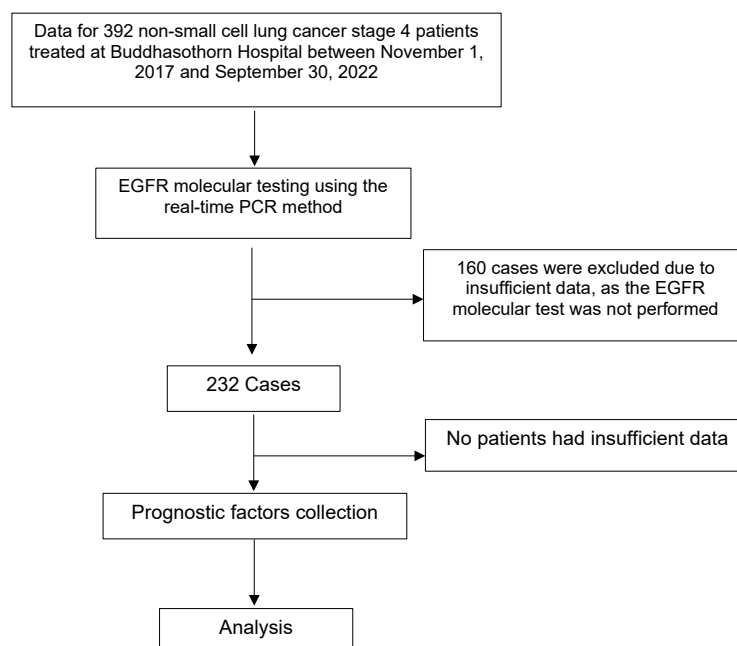


Figure 1. Study flow diagram

Table 2. Frequency of EGFR mutations in non-small cell lung cancer (NSCLC)

EGFR	Number (%) N = 232
EGFR wild type	124 (53.45)
EGFR mutation	108 (46.55)
Type of EGFR mutation	Number (%) N = 108
Exon 19 deletion	56 (51.85)
Exon 21 L858R mutation	39 (36.11)
Uncommon EGFR mutation	5 (4.63)
Dual common EGFR mutation	3 (2.78)
EGFR exon 20 insertions	2 (1.85)
Common EGFR mutation plus primary T790M mutation	2 (1.85)
Primary EGFR T790M mutation	1 (0.93)

showed that the EGFR wild type was present in 124 cases, comprising 53.45% of the total. Among those cases, 81 were male (65.32%) and 43 were female (34.68%). Notably, 63.71% of the EGFR wild type cases were smokers, while 36.29% were non-smokers. Regarding NSCLC subtype distribution, adenocarcinoma predominated at 83.26%, followed by squamous cell carcinoma at 14.52%, with other cell types comprising 2.42%. Conversely, EGFR mutation was found in 108 cases, making up 46.55% of the total. Within the EGFR mutation group, 40 were male (37.04%) and 68 were female (62.96%). Moreover, 27.78% of EGFR mutation cases were smokers, while 72.22% were non-smokers. Remarkably, NSCLC consisted primarily of adenocarcinoma, observed in 99.07% of cases, with squamous cell carcinoma identified in only 0.93%. No other cell types were detected (Table 3).

Gender, smoking history, and lung cancer subtype are considered clinical factors associated with EGFR mutation in NSCLC. This study included

124 cases in the EGFR wild type group and 108 cases in the EGFR mutation group. Among female participants, 68 cases (62.96%) had EGFR mutation, which was higher than the 43 cases (34.68%) in the EGFR wild type group. Among male participants, 40 cases (37.04%) had EGFR mutation, which was lower than the 81 cases (65.32%) in the EGFR wild type group. Among non-smokers, 78 cases (72.22%) had EGFR mutation, higher than the 45 cases (36.29%) in the EGFR wild type group. Among smokers, 30 cases (27.78%) had EGFR mutation. Additionally, there were 107 cases (99.07%) with the EGFR mutation adenocarcinoma subtype, which is higher than the 103 cases (83.06%) in the EGFR wild type group. Only 1 case (0.93%) of squamous cell carcinoma had EGFR mutation, while there were 18 cases (14.52%) in the EGFR wild type group. No other subtypes showed EGFR mutation; however, only 3 cases (2.42%) were found in the EGFR wild type group (Table 3).

In univariable regression analysis, factors associated with detecting EGFR mutation were identified. Female gender, a history of not smoking, adenocarcinoma subtype lung cancer, and bone metastasis were among the factors identified. Additionally, there was a statistically significant decrease in the detection of EGFR mutation, particularly in cases of squamous cell carcinoma. Subsequently, multivariable regression analysis confirmed that non-smokers and the adenocarcinoma subtype of lung cancer remained significant independent factors in EGFR mutation detection (Table 4).

Survival analysis indicated that patients with stage 4 NSCLC had a median overall survival of 13.57 months (95%CI 10.56-15.15). Comparing the

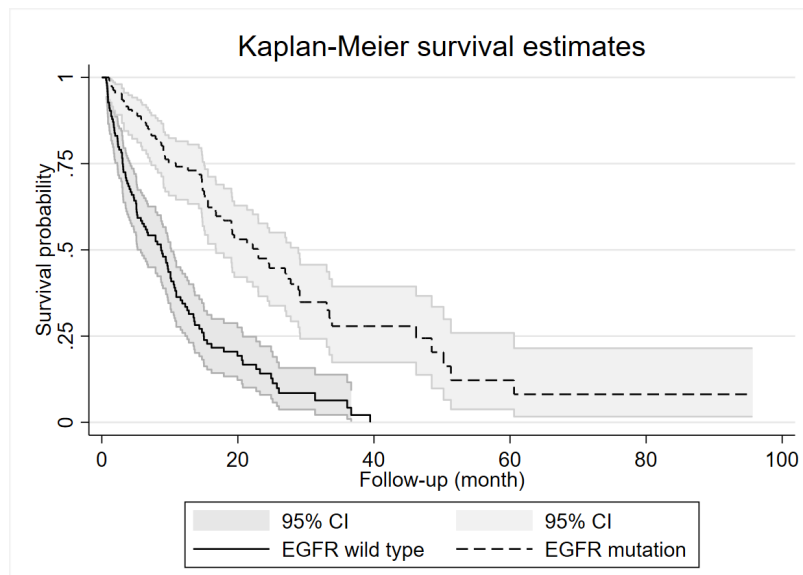
Table 3. The relationship between detecting EGFR mutation and clinical factors

	EGFR wild type N=124 (%)	EGFR mutation N=108 (%)	p-value
Gender			
Male	81 (65.32)	40 (37.04)	<0.001
Female	43 (34.68)	68 (62.96)	<0.001
Smoking			
Former/current smoker	79 (63.71)	30 (27.78)	<0.001
Never-smoker	45 (36.29)	78 (72.22)	<0.001
Type of NSCLC			
Adenocarcinoma	103 (83.06)	107 (99.07)	<0.001
Squamous cell carcinoma	18 (14.52)	1 (0.93)	<0.001
Other types	3 (2.42)	0 (0.00)	0.250

Table 4. Results of univariable and multivariable regression analyses of potential clinical variables as independent predictors of EGFR mutation in NSCLC

	Univariable analyses			Multivariable analyses		
	uOR	95% CI	p-value	aOR	95% CI	p-value
Female	3.20	1.87-5.48	<0.001	1.32	0.56-3.11	0.517
Non-smoker	4.56	2.61-7.97	<0.001	2.84	1.20-6.74	0.018
Age ≥ 60 years	0.77	0.45-1.32	0.342	0.78	0.42-1.45	0.439
Adenocarcinoma	21.82	2.88-165.15	0.003	14.39	1.77-116.84	0.013
Squamous cell carcinoma	0.06	0.01-0.42	0.005	1 (omitted)		
Other types	1 (omitted)			1 (omitted)		
Brain metastasis	0.58	0.30-1.13	0.112	0.57	0.27-1.22	0.145
Lung to lung metastasis	1.76	0.89-3.44	0.102	1.50	0.67-3.35	0.329
Pleural metastasis	1.64	0.97-2.75	0.063	1.50	0.81-2.78	0.201
Liver metastasis	1.52	0.76-3.06	0.241	1.10	0.49-2.47	0.818
Bone metastasis	1.98	1.13-3.45	0.016	1.63	0.86-3.10	0.134

uOR, unadjusted odds ratio; aOR, adjusted odds ratio; CI, confidence interval

**Figure 2.** Kaplan-Meier survival analysis according to EGFR status

EGFR wild type and mutation groups, the mutation group had a median overall survival of 22.98 months (95%CI 16.79-28.89), compared to 8.72 months (95%CI 5.74-10.20) for the wild type group. The results showed significant survival differences between patients with EGFR mutations and EGFR wild-type (median survival time difference 12.60 months, 95% CI: 7.78-17.42, $p < 0.001$). **Figure 2** shows the Kaplan-Meier curve for EGFR status.

DISCUSSION

EGFR mutation was identified in approximately 47% of cases. Within the non-smoker group, EGFR mutation prevalence was notably higher at 63%, compared to around 28% in the smoking group. The frequencies of EGFR mutation types

were predominantly around 90%, consisting of common mutations such as exon 19 deletion and exon 21 L858R. This indicates a significant association between smoking status and EGFR mutation rates, with distinct patterns observed in different subgroups.

We examined the relationship between EGFR mutation and various clinical factors in NSCLC patients. Our analysis, conducted using logistic regression, revealed significant associations of adenocarcinoma and non-smoking status with EGFR mutation in both univariable and multivariable analyses. Demographic characteristics, tumor features, and clinical metastatic site were thoroughly assessed using statistical analysis techniques to determine their association with EGFR mutation. Adenocarcinoma presented the highest risk (ad-

justed odds ratio [aOR] 14.39, 95%CI 1.77-116.84, $p = 0.013$), followed by non-smoking status (aOR 2.84, 95%CI 1.20-6.74, $p = 0.018$). Understanding the influence of adenocarcinoma and non-smoking status is imperative for predicting EGFR mutation, providing valuable insights for personalized treatment strategies.

Lung cancer in never-smoker Asian females represents a distinct clinical entity, with the majority of these cancers arising from oncogenic mutations. Specifically, in female Asian non-smokers with adenocarcinoma lung cancer, there is a 70-80% association with identifying oncogenic mutations. Among these mutations, EGFR mutations are frequently associated with older age and a predominantly acinar pattern, while ALK rearrangements are principally associated with younger age and a predominantly solid pattern (12).

The data suggest that three main factors—female gender, non-smoking, and adenocarcinoma subtype—are associated with EGFR mutation detection (13-15). The influence of gender on EGFR mutation detection may stem from hormonal receptors. A meta-analysis found a correlation between high nuclear expression of ER-beta and EGFR mutation in non-small cell lung cancer, supporting the role of hormone receptors in mutation development (16, 17). Scientific evidence from epidemiological studies and molecular analyses has been reported regarding the differences in molecular pathways between smokers and non-smokers (18-20). Smoking has been shown to lead to significant differences in genetic alterations compared to non-smokers, such as the up-regulation of genes like the AKR1B10 gene from the aldo-keto reductase superfamily (AKR), which is consistently found in smokers (21-23). Additionally, observational studies have reported the presence of EGFR mutations in smokers. Therefore, smoking is likely an important environmental factor influencing EGFR mutations, as indicated by numerous studies in the field (24, 25).

According to the available data, adenocarcinoma lung cancer is observed predominantly in females who do not smoke. This may suggest a correlation with the detection of EGFR mutations.

One limitation of this study is that the observed frequency of EGFR mutations may not accurately represent the true prevalence. This discrepancy

arises from the exclusion of approximately 40% of the cohort due to the absence of EGFR molecular testing, a procedure reimbursable in Thailand since 2021. Despite its limitations, this study contributes significant insights. This research provides preliminary evidence suggesting a higher prevalence of EGFR mutations among Thai populations, including both smokers and nonsmokers, compared to Western countries.

CONCLUSIONS

Adenocarcinoma and non-smoking status represent significant factors associated with EGFR mutation. Additionally, targeted therapy designed for EGFR mutation is accessible for lung cancer treatment. In Thailand, reimbursement for first-line therapy is available, enabling access to targeted therapy customized for EGFR mutation in lung cancer treatment. Therefore, in the case of individuals diagnosed with adenocarcinoma and no history of smoking it may be appropriate to consider EGFR mutation during the exploration of personalized treatment options. However, research data suggests that patients with squamous cell carcinoma and/or a history of smoking may also harbor EGFR mutations. Thus, testing for EGFR mutations before initiating treatment is crucial to ensure precise therapeutic approaches.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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