Original Article

The Relationship between Smoking History with ECOG Score, EGFR Mutation Status, and Clinicopathology Data of NSCLC Patients: Preliminary Study

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Abstract

Background: Patients with non-small cell lung cancer (NSCLC) have a poor outcome. Mutations in the EGFR gene play a crucial role in determining treatment options and prognosis. Smoking history, clinicopathological features, including patient performance, and EGFR gene mutation have served as clinical guidelines for monitoring. This study aims to examine the association between smoking history and ECOG score, EGFR mutation status, and clinicopathological characteristics of patients with NSCLC in Yogyakarta.

Methods: An observational and analytic study, with a retrospective cohort design from 32 patients diagnosed with NSCLC. Data on smoking history, clinicopathological characteristics, ECOG performance scores, and EGFR mutation types (Exon 19 deletion and Exon 21 L858R) were extracted and concluded from medical records. The relationship between these variables was analysed using the Chi-square test.

Results: The analysis began by exploring the relationship between smoking history and initial ECOG performance scores. It was discovered that non-smokers exhibited poorer initial ECOG scores (P=0.025). Smoking history was significantly associated with specific EGFR mutation types (P=0.009), but not with overall EGFR mutation status. The analysis revealed that deletions on Exon 19 were mainly found in patients who smoked, whereas mutations in Exon 21 were uniquely present in non-smokers. Clinical follow-up also shows an association (P=0.002). This finding suggests that smoking behaviour interferes with the carcinogenesis of NSCLC.

Conclusion: The relationship between smoking history, performance status, exon-specific EGFR mutations, and clinical follow-up suggests differences in the carcinogenic mechanisms of NSCLC exon-specific mutations, highlighting biological diversity and emphasizing the need for detailed molecular studies to improve prognostic accuracy.

Keywords: ECOG, EGFR mutation, non-small cell lung carcinoma, smoking history

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INTRODUCTION

Lung cancer represents a significant global health issue, being the foremost cause of cancer-related mortality worldwide. It primarily manifests in two major forms, with Non-Small Cell Lung Cancer (NSCLC) being the most prevalent. The management of lung cancer still requires improvement, so it is essential to understand the factors that predict disease progression and patient response to treatment. This enables clinicians to develop more effective management plans and enhance patient survival.[1–3]

Several key factors can help clinicians more effectively manage lung cancer patients' clinical pathways, one of which is the Eastern Cooperative Oncology Group (ECOG).[4,5] ECOG performance status is a tool comprising five criteria that assess the daily activity levels of cancer patients with a six-point numerical scale, that is zero (0) normal functional status; one (1) capable in light activities; two (2) can only perform self-care; three (3) only limited self-care; four (4) completely disabled; five (5) dead.[6] It helps clinicians to determine if a patient is capable of handling treatments, such as chemotherapy and targeted therapy.[7]

Besides that, looking at the risk factors for lung cancer, it is known that smoking is a significant risk factor, because there are many carcinogenic substances in the smoke. When they interact with mucosal and stromal cells, they trigger carcinogenic pathways. Carcinogenic substances related to smoking may alter the molecular pathway of cancer and affect how well treatments work and how doctors plan patient care. Smoking is also a predictive and prognostic factor related to other factors that affect lung cancer management.[8]

In NSCLC patients, Epidermal Growth Factor Receptor (EGFR) mutations are a common pathway found without a history of smoking. Common mutations included Exon 19 deletions and Exon 21 (L858R). Individuals with these genetic mutations may respond to EGFR tyrosine kinase inhibitors (TKIs). Therefore, testing for EGFR mutations is also crucial for clinicians to determine the appropriate treatment and forecast the patient's prognosis.[9]

This study aimed to determine how smoking history is related to patient clinicopathology characteristics, including patients' performance status, EGFR mutation, and clinical follow-up in patients with non-small cell lung cancer (NSCLC).

METHODS

The study was conducted at the Medical Records Department and the Anatomical Pathology Laboratory of Bethesda Hospital, Yogyakarta, by reviewing medical records from 2018 to 2024. The medical records and EGFR mutation test results were from the same laboratory, was conducted from May 2025 to July 2025. The EGFR mutation tests and specific exon mutation were studied from the Department of Anatomical Pathology's records.

The study population included adult patients (≥18 years old) with confirmed adenocarcinoma-type NSCLC. The inclusion criteria were adult patients (18 years or older) with a confirmed pathological diagnosis of pulmonary adenocarcinoma and available EGFR immunohistochemistry (IHC) test results, including exon type by PCR examination. Exclusion criteria were patients with small cell lung carcinoma, squamous cell carcinoma, mixed histopathology, or incomplete clinical data.

This retrospective, observational, analytic study included 32 patients with NSCLC. The sample size followed the commonly accepted rule of thumb for a pilot study, which recommends a minimum of 30 subjects to provide preliminary statistical power and allow estimation of effect sizes for future confirmatory research.[9]

For the analysis of demographic and clinicopathological data, 32 medical records were obtained from the medical records department. The recorded data include demographic variables such as age, sex, smoking history, and clinicopathological variables such as tumor stage, Karnofsky Performance Scale (KPS), ECOG performance score (ECOG PS), EGFR immunohistochemistry (IHC) data with exon type mutation, and therapy data, as well as clinical follow-up period data.

Smoking history was documented based on information provided in the clinician's cytopathology examination request form and corroborated by the patient's medical records. Smoking history is divided into non-smokers (never smoked) and smokers (current or former smokers).

Tumor stage was determined from radiological data and the medical record at the patient's initial presentation of the disease during the first visit to the Pulmonology Clinic. The lung cancer staging was according to the Eighth Edition Lung Cancer TNM classification. The staging is classified into two parts: one in which metastasis to distant organs has not occurred, and another in which it has.[10]

Karnofsky Performance Scale and ECOG PSwere assessed based on the patient's symptoms and clinical signs at the initial visit to the Pulmonology Clinic and at the conclusion of the documented follow-up period. The assessment of KPS and ECOG PS adheres to established guidelines and is based on anamnesis, physical examination, and comorbidities. This evaluation does not correspond to specific periods of clinical follow-up observation, as its objective is to ascertain the relationship between the initial and final performance statuses and other related factors. The final KPS and ECOG PS were

assessed based on the last recorded time of the patient's clinical follow-up in the medical record.

Descriptive statistics summarized patient characteristics, while the Chi-square test was utilized to analyze correlations between clinicopathological factors and EGFR mutation status. A value of *P* below 0.05 was used to establish statistical significance. When any cell value in the table falls below the expected count, the likelihood ratio is used to assess significance. Software IBM SPSS Statistics 25 was used to analyse the results.

Ethical approval was obtained from the Health Research Ethics Committee (KEPK) of Bethesda Hospital, Yogyakarta (number 34/KEPK-RSB/IV/25).

RESULTS

This study employed a retrospective cohort comprising 32 individuals diagnosed with NSCLC. Although the relatively small sample size limited the statistical power and generalizability of the findings, it nonetheless offered valuable insights into this patient population.

The population was primarily composed of older males, many of whom presented with a high stage of disease at initial diagnosis and significant deterioration of functional limitations at the end of clinical follow-up compared to initial clinical follow-up.

The EGFR mutations were highly prevalent, with Exon 19 deletions appearing more frequently than Exon 21 L858R mutations. This molecular profiling directly guided the widespread use of target therapies (TKIs) such as gefitinib over traditional chemotherapy. The baseline patient characteristics are presented in Table 1.

The data demonstrated a profound connection between a patient's molecular profile and the therapy they received. Every patient identified with an EGFR mutation was prescribed the first-generation EGFR-TKI gefitinib. This consistency underscores strict adherence to clinical guidelines that prioritize EGFR-TKIs as the standard of care for mutation-positive NSCLC. Patients with EGFR mutations more often had very low (or worse) final Karnofsky scores than those without EGFR mutations.

Table 1. Baseline Characteristics of Patients

Variables	n	%
Age		
<60 years	10	31.2
≥60 years	22	68.8
Sex		
Male	23	71.9
Female	9	28.1
Smoking history		
Not smoking	17	53
Smoking	15	46
Initial Karnofsky score		
80	3	9.4
70	6	18.8
60	4	12.5
50	6	18.8
40	8	25
30	5	15.6
Final Karnofsky score		
60	2	6.3
50	1	3.1
40	7	21.9
30	9	28.1
20	5	15.6
10	3	9.4
0	5	15.6
Initial ECOG score		
1	9	28.1
2	10	31.3
3	13	40.6
Final ECOG score		
2	3	9.4
3	15	46.9
4	9	28.1
5	5	15.6
Metastasis		
Distance metastasis (-)	11	34.4
Distance metastasis (+)	21	65.6
Number of Metastasis locations		
0	5	15.6
1	17	53.1
2	8	25
3	2	6.3
Mutation EGFR status		
EGFR mutation	20	62.5
No EGFR mutation	12	37.5
Exon EGFR-specific mutation		
Exon 19	11	34.4
Exon 21	5	15.6
Not detected	12	37.5
No data	4	12.5
Therapy		
EGFR-TKI	19	59.4
Chemotherapy and/or radiotherapy	13	40.6
Clinical follow-up		
<30 weeks	7	21.8
30–<60 weeks	13	40.6
60–<90 weeks	5	15.7
≥90 weeks	7	21.9

Table 2. The Relationship of Smoking History with Clinical and Molecular Variables

Variable	Not smoking	Smoking	*P*
Age			
≤60 years	5	5	0.811
>60 years	12	10	
Sex			
Male	9	14	0.011
Female	8	1	
Initial Karnofsky score			
80	1	2	
70	4	2	
60	1	3	0.031
50	1	5	
40	5	3	
30	5	0	
Final Karnofsky score			
60	4	1	
50	0	1	
40	4	3	
30	3	6	0.558
20	3	2	
10	2	1	
0	4	1	
Initial ECOG score			
1	5	4	
2	2	8	0.025
3	10	3	
Final ECOG score			
2	1	2	
3	7	8	0.547
4	5	4	
5	4	1	
EGFR mutation status			
Mutation	10	10	0.647
Not mutation	7	5	
Exon-specific Gene EGFR mutation			
Exon 19	3	8	
Exon 21	5	0	0.009
Not detected	7	5	
Therapy			
EGFR-TKI	9	10	
Chemotherapy and/or radiotherapy	8	5	0.430
Clinical follow-up			
≥90 weeks	7	0	
60 - <90 weeks	4	1	0.002
30 - <60 weeks	4	9	
<30 weeks	2	5	
Stage			
Low	7	4	0.388
High	10	11	
Number of Metastasis locations			
0	4	1	
1	10	7	0.132
2	3	5	
3	0	2	

The study identified a significant relationship between smoking history and initial performance status. Interestingly, non-smokers in this group generally presented with lower baseline performance scores (ECOG 3) compared to smokers, who more frequently occupied the better initial category (ECOG 2). This trend was consistent across both the ECOG and Karnofsky scales. However, the impact of smoking on physical function appears to diminish over time. By the end of the study, there was no longer a meaningful link between smoking history and the final performance scores.

While smoking did not determine whether a patient had an EGFR mutation in general, it played a critical role in the specific type of mutation present. This observed that Exon 19 deletions were the predominant finding in smokers, whereas Exon 21 mutations were found exclusively in the non-smoking cohort. Clinical management has followed established guidelines, as all patients identified with these mutations received targeted EGFR-TKI therapy (gefitinib).

Smoking history was also a clear determinant of sex distribution and follow-up duration. Men were significantly more likely to be smokers, while women were predominantly non-smokers. Notably, non-smokers benefited from more extended clinical follow-up periods, suggesting a more favorable overall trajectory compared to the smoking group. A summary of these associations is presented in Table 2.

Neither initial nor final ECOG performance status showed a significant relationship with overall EGFR mutation status. This finding is somewhat unexpected, given the known efficacy of TKIs in NSCLC patients with EGFR mutations. The final Karnofsky score was significantly associated with the duration of clinical follow-up, suggesting that performance status maintained late in the disease course is a positive prognostic indicator.

DISCUSSION

The results indicated that smoking has molecular pathways that interfere with the mutation of the EGFR gene, even in the EGFR mutation, which causes a specific exon mutation.[11,12]

Table 3. Correlations Between Main Clinical and Molecular Factors (value of *P*)

Variable Dependent	Initial ECOG score	Final ECOG score	Declining ECOG score	EGFR mutation	Clinical follow-up
Age	0.283	0.504	0.325	0.325	0.844
Sex	0.788	0.377	0.282	0.54	**0.033#**
Smoking history	**0.028#**	0.547	0.430	0.647	**0.001#**
Initial Karnofsky score	N/A*	N/A*	N/A*	0.620	0.266
Final Karnofsky score	N/A*	N/A*	N/A*	**0.009#**	**0.021#**
Stage of disease	0.282	0.183	0.246	0.149	0.501
Number of Metastasis locations	0.214	0.749	0.467	0.271	0.311
Exon-specific EGFR mutation	0.18	0.816	0.572	**0.0001**	0.437
Therapy	0.526	0.176	0.348	**0.0001**	0.926

*Note: N/A indicates that a direct correlation was not analyzed because the variables measure the same category.

The smokers had an Exon 19 deletion predominant, and the non-smokers had an Exon 21 mutation predominant. Therefore, smoking and EGFR mutations might be related at the exon level, suggesting how smoking affects the tumors.[11,12] The Exon 19 deletion was more frequently observed in smokers, while the Exon 21 mutation was found only in non-smokers. Doing detailed molecular profiling is crucial because the prevalence of the population in smokers underscores the molecular heterogeneity influenced by smoking.[13–16]

Non-smokers had an initial KPS and ECOG PS worse than smokers, but smokers and patients with lower final Karnofsky scores showed shorter clinical follow-up periods. The analysis of non-smokers showed worse initial ECOG scores, unlike most prior studies.[17] The small sample size bias, the uniqueness of the non-smokers' disease, or other factors that were not known or controlled in the research might affect the studies.[11,18–20] However, there was no association between smoking history and the final ECOG score (*P*=0.547).

The more severe manifestations of the disease occur in non-smokers. This could be due to EGFR-TKI therapy and prolonged overall survival. However, this prolonged ultimately led to a state of resistance and functional decline that non-EGFR mutational patients may not experience. Additionally, a later diagnosis in a non-smoker could occur due to a lack of awareness of their condition.[21,22] Therefore, the impact of smoking on patients' performance might worsen over time due to the progression of cancer, or if EGFR-TKI treatment is effective, they were more likely to be observed during the natural performance function decline of late-stage disease.[11]

The absence of a significant correlation between the overall EGFR mutation status and both initial and final ECOG scores was noteworthy. This could be attributed to the timing of the final ECOG assessment during the phase of EGFR-TKI resistance, heterogeneity in patient responses, or the small sample size.[23] This was unexpected, given how well TKIs work in NSCLC with EGFR mutations.[17]

This might occur because patients had already developed EGFR-TKI resistance at the time the final ECOG was taken, due to differences in baseline characteristics between patients, or because of the small sample size. Other factors, such as tumor size at EGFR-TKI initiation, the presence of extrathoracic metastases, and tumor mutational burden, might matter more for the ECOG score.[24,25] Therefore, EGFR mutations did not really determine patients' functional status in this group.[11]

The paradoxical association between EGFR mutation status and worse final Karnofsky scores may highlight the difficulties posed by TKI resistance and subsequent disease progression. This is because the final Karnofsky score was assessed when the cancer cells might have developed EGFR-TKI resistance, and the disease had progressed. Another reason is that patients with EGFR mutations who received EGFR-TKI treatment survive longer and are more prone to functional decline.[13,23,26,27] Patients who had better final Karnofsky scores tended to have longer follow-up, showing that performance status late in the disease is a good sign.[24]

This study carries several clinical implications, particularly in the realm of personalized medicine. Comprehensive molecular testing, including specific

exon analysis, is crucial for guiding EGFR-TKI therapy and understanding its association with smoking history.[10] All 19 patients with EGFR mutations received EGFR-TKI therapy, consistent with the guidelines.[28] The EGFR-TKI used in this study was first-generation gefitinib.

The notable correlation between smoking and specific exon mutations, alongside its influence on the duration of follow-up, highlights the critical importance of counseling for smoking cessation.[11,29] Although the initial ECOG status may reveal unexpected correlations, the final performance status remains a dependable prognostic indicator. Clinicians should recognize the evolving nature of performance status in the context of targeted therapy and resistance.

LIMITATION

There were several limitations for this study, such as a small sample size (total sample 32 subjects) that limited statistical power and generalizability. Second, this study was a single-center data study, which might introduce potential institutional biases. Next, this study design was a retrospective study, which was more prone to bias, such as incomplete data. Then, the lack of detailed clinical data, such as granular information (e.g., specific stage, comorbidities, and duration of TKI response), might limit the explanation of paradoxical findings. Last, ambiguous variable definitions, such as vague definitions for “smoking history” and the timing of ECOG/Karnofsky assessments, might affect interpretation.

CONCLUSION

The preliminary findings of this report revealed a notable yet surprising link between smoking history and initial ECOG status in non-smokers. Additionally, specific EGFR exon mutations demonstrated a strong correlation with smoking history, with Exon 21 mutations predominantly found in non-smokers, and Exon 19 deletions were more common in smokers. However, no significant relationship was observed between the overall EGFR mutation status and ECOG scores. EGFR-TKI therapy strongly correlates with EGFR mutation status. The paradoxical finding of worse final Karnofsky scores in patients with EGFR mutations warrants further investigation.

Suggest that larger multi-center prospective studies are needed for better validation and generalization. Also recommend investigating specific molecular mechanisms that explain the association between smoking and EGFR exon mutations. Further research on baseline disease burden, comorbidities, and diagnostic pathways can be added to evaluate the factors affecting initial performance status. Longitudinal observation of performance status using ECOG/Karnofsky assessments is necessary to understand dynamic changes in response and resistance. Lastly, a more comprehensive integration of clinical and laboratory data (e.g., EGFR mutations) is needed to achieve a holistic understanding of prognostic factors.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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