Original Article

Risk Factors for EGFR (Epidermal Growth Factor Receptor) Gene Mutations in Lung Adenocarcinoma Patients at Arifin Achmad Hospital, Riau Province

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Abstract

Background: Lung cancer is the first cause of oncological death worldwide. Guidelines made by various cancer associations, including PDPI-IASTO, regarding NSCLC recommend that all advanced stages of NSCLC undergo target genetic testing, such as EGFR mutations. The incidence of EGFR mutations in Asian populations is quite high.

Methods: This was a retrospective observational analytic study with a cross-sectional study design.

Results: The most unmodifiable risk factors were age ≥45 years (81.4%), male sex (70.6%), location of lung cancer on the right (52.9%), cancer size of ≥5 cm (100%), M1a metastases (57.8%), and no family history of malignancy (97.1%). The smoking status (ex-smoker) (*P*=0.022; OR=4.3; 95% CI=1.24-15.57), sex (male) (*P*=0.007; OR=3.409; 95% CI=1.406-8.268), and metastatic status (M1a) (*P*=0.025; OR=0.203; 95% CI=0.05-0.821) were the dominant risk factors that affected the incidence of EGFR mutations in patients with lung adenocarcinoma at Arifin Achmad Hospital.

Conclusion: Male, ex-smokers, and metastatic status (M1a) were the dominant risk factors for the incidence of EGFR mutations in lung adenocarcinoma patients at Arifin Achmad Hospital.

Keywords: EGFR, gene mutation, lung adenocarcinoma

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INTRODUCTION

Lung cancer is the first cause of oncological death worldwide. Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer, with a case presentation of 80-85% compared to Small Cell Lung Cancer (SCLC), which accounts for 10 to 15%. NSCLC is divided into adenocarcinoma (ADC) for up to 50% and squamous cell carcinoma (SCC) for 30%.[1,2]

Lung cancer therapy modalities have evolved in line with the development of biomolecular technology. The classification of NSCLC that was previously known has evolved from histological to molecular subtypes. Histological types of adenocarcinomas, squamous cell carcinoma, and large cell carcinoma also have their molecular types, such as Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), Receptor Tyrosine Kinase 1 (ROS1), and so on, in line with the development of molecular-based studies. Changes in the assessment of NSCLC based on histological appearance to molecular ones encourage clinicians to use this molecular-based modality in the management of lung cancer patients.[3,4]

Phenotypic and genotypic diagnostics play an important role in the management of lung cancer. In Indonesia, molecular-based therapy, known as targeted therapy, began to be used in the early 2000s, whereas previously only chemotherapy, radiotherapy, surgery, and combination therapy modalities were used. Several targeted therapies that were being developed at that time were EGFR-mAb, EGFR-TKI (Tyrosine Kinase Inhibitor), ALK, and ROS1. However, the targeted therapy that has been implemented at Arifin Achmad Hospital is the first generation of EGFR-TKI, i.e. Gefitinib.[5]

Guidelines made by various cancer associations including, PDPI-IASTO (*Perhimpunan Dokter Paru Indonesia* – Indonesian Association for the Study on Thoracic Oncology), regarding NSCLC recommend that all advanced stages of NSCLC undergo target genetic testing, such as EGFR mutations.[6,7]

However, tumor sampling for EGFR mutation testing is risky, expensive, and not suitable for all patients. The EGFR mutation test can also produce a false-negative result. Thus, EGFR mutation status can be identified earlier without molecular examination by screening the risk factors.[8]

The incidence of EGFR mutations in Asian populations is quite high. The incidence of EGFR mutations in Asians (Japanese) is close to 30%, higher than in the white population, which is 20%. [9,10] The incidence of EGFR mutations in Indonesia is 44.5%, followed by an incidence in Dharmais Cancer Hospital Jakarta of 34%.[11,12]

However, there is no study related to this has been carried out at the Arifin Achmad Hospital Pekanbaru. Gene mutation in EGFR has been identified in various studies to be strongly associated with clinical factors of the patient, such as East Asian racial origin, female sex, non-smoker, and adenocarcinoma type. [13,14]

It has been reported that smoking is an independent prognostic factor in EGFR gene mutations. Previous studies have reported a relationship between smoking history and therapy resistance, and patients with NSCLC who have EGFR mutations have a history of smoking.[15] Lung inflammation and comorbidities cause an increase in pro-inflammatory cytokines that accelerate cancer development and instability of IGF levels, which ultimately induce EGFR mutations.[16] Chest CT scan with the appearance of a tumor accompanied by GGO (ground glass opacity), air bronchogram, non-smoker status, and female sex were significantly associated with EGFR mutations.[17]

Based on the research and guidelines of the thoracic oncology organization, as well as the high incidence of EGFR mutations in patients with lung adenocarcinoma in East Asia and Indonesia and also the high cost and time-consuming EGFR mutation test and not suitable for various groups of patients related to health insurance regulations, the identification of early risk factors is an important component. This study was conducted for on the risk factors for EGFR mutations in patients with pulmonary adenocarcinoma at Arifin Achmad Hospital.

METHODS

This was a retrospective observational analytic study with a cross-sectional design. The target population of this study was all lung adenocarcinoma patients at Arifin Achmad Hospital Pekanbaru from June 2018 to June 2022. The subjects of this study were all lung adenocarcinoma patients who underwent EGFR mutation biomolecular examination at Arifin Achmad Hospital Pekanbaru.

This research used consecutive sampling to select the study subjects. The minimal sample for this study was 63 study subjects. The inclusion criteria for this study were lung adenocarcinoma patients who underwent biomolecular examination for EGFR mutations at Arifin Achmad Hospital Pekanbaru. Meanwhile, the exclusion criteria were patients with incomplete medical record data and who were known to have or experienced cancer other than lung adenocarcinoma.

Additionally, this study examined diagnostic errors and delays among the lung adenocarcinoma patients. Diagnostic errors were defined as inaccuracies in the interpretation of EGFR mutation biomolecular results or other clinical diagnostic mistakes recorded in the patient's medical records. Diagnostic delays were measured from the time patients first reported symptoms to the time a lung adenocarcinoma diagnosis was confirmed, as well as from the time of the biomolecular examination to the receipt of the results by the treating physician. All data were collected, then tabulated and statistically analyzed using the computer program SPSS version 21.0 with a 95% confidence interval and a significance rate of 0.05 (P=0.05).

RESULTS

For the period June 2018 to June 2022, 102 patients with lung adenocarcinoma at the Arifin Achmad Pekanbaru Hospital met the inclusion and exclusion criteria.

Table 1. An overview of non-modifiable and modifiable risk factors

Variable	N	%
Unmodifiable risk factors		
Age		
<45 years	19	18.6
≥45 years	83	81.4
Sex		
Male	72	70.6
Female	30	29.4
Family History of Malignancy		
No	99	97.1
Yes	3	2.9
Cancer location		
Right	54	52.9
Left	48	47.1
Cancer size		
<5 cm	0	0.0
≥5 cm	102	100
Metastatic status		
M0	11	10.8
M1a	59	57.8
M1b	19	18.6
M1c	13	12.7
Modifiable risk factors		
Smoking Status		
Non-smoker	32	31.4
Smoker	22	21.6
Ex-smoker	48	47.1
Comorbidities		
No	86	84.3
Yes	16	15.7
Nutritional Status		
Underweight	76	74.5
Normoweight	26	25.5
Overweight	0	0.0
Obese	0	0.0
Occupation		
Non-farmer	92	90.2
Farmer	10	9.8
EGFR mutation status		
Wild type	62	60.8
Exon 18 subs	2	2.0
Exon 19 del	19	18.6
Exon 20 T970M	1	1.0
Exon 21 L858R	14	13.7
Multiple	4	3.9

In this study, the most unmodifiable risk factors found were age >45 (81.4%), male sex (70.6%), location of lung cancer on the right (52.9%), cancer size ≥5 cm (100%), M1a metastases (57.8%), and no family history of malignancy (97.1%). The most modifiable risk factors found were ex-smokers (47.1%), did not have comorbidities (84.3%), had malnutrition status, i.e., with a BMI of <18 (74.5%), and were non-farmers (90.2%). The most common EGFR mutation status was wild-type (60.8%), followed by EGFR mutations exon 19 del (18.6%), and exon 21 L858R (13.7%).

The highest prevalence of metastatic status in lung adenocarcinoma patients at Arifin Achmad Hospital Pekanbaru for the period of June 2018 to June 2022 was M1a (malignant pleural effusion or pericardial effusion, nodules in the pleura or pericardium, or nodules in the contralateral lobe), which accounted for 59 subjects (57.8%), followed by single extrathoracic metastases or M1b in 19 subjects (18.6%), multiple extrathoracic or M1c metastases in 13 subjects (12.7%), and no metastases or M0 in 11 subjects (10.8%). Figure 1 shows an overview of the prevalence of metastatic status.

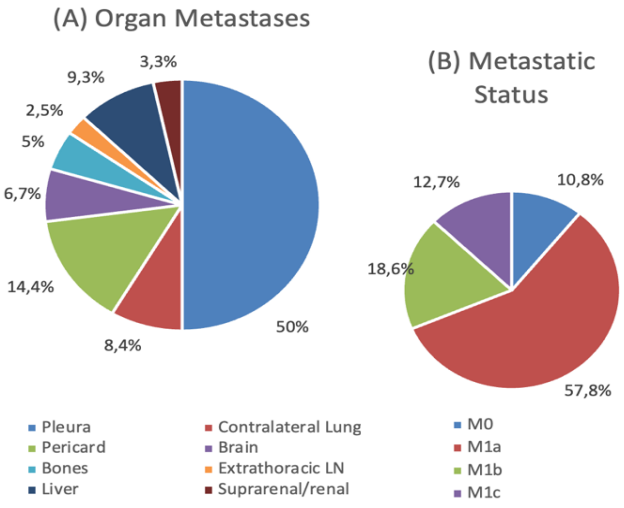

Figure 1. (A) Organ Metastases, (B) Metastatic Status

Metastases 1a (M1a) has the highest prevalence of metastatic status, as shown in Figure 1. Based on the division of organs in M1a, the pleura was the most common location for metastatic organs found in our study (50%) of lung adenocarcinoma patients. The highest prevalence of M1a metastatic

organs was the pleura in 59 subjects (50%), then pericardium in 17 subjects (14.4%), and 10 contralateral lung nodules (8.4%). The prevalence of metastases in other organs found was in the liver for 11 subjects (9.3%), brain for 8 subjects (6.7%), bones (costa, vertebrae, etc.) for 6 subjects (5%), suprarenal/renal for 4 subjects (3.3%), and extrathoracic lymph nodes in 3 subjects (2.5%). Figure 1 shows an overview of the prevalence of organ metastases.

Based on Table 1, 16 subjects (15.7%) had comorbidities. Hypertension was the most common comorbid found in this study, with 14 subjects (37.8%), followed by dyslipidemia in 13 subjects (35.1%), and diabetes mellitus in 10 subjects (27%). The highest EGFR mutation prevalence was found in exon 19 dels with 19 subjects (18.6%), followed by exon 21 L858R with 14 subjects (13.7%).

Other prevalences were found in exon 18 subs mutations in 2 subjects (2%), exon 20 T790M in 1 subject (1%), and multiple exon mutations in 4 subjects (3.9%). Figures 2 and 3 show comorbidities and status of EGFR mutations.

Table 2. The relationship between risk factors and the occurrence of EGFR mutations in patients with lung adenocarcinoma at Arifin Achmad Hospital

Variable	Non-mutation (N=62)		Mutation (N=40)		Total (N=102)		*P*
	N	%	N	%	N	%	
Unmodifiable risk factors							
Age							
<45 years	12	11.8	7	6.9	19	18.6	0.814
≥45 years	50	49.0	33	32.4	83	81.4	
Sex							
Male	50	49	22	21.6	72	70.6	0.006*
Female	12	11.8	18	17.6	30	29.4	
Family history of malignancy							
No	60	58.8	39	38.2	99	97.1	0.661[a]
Yes	2	2.0	1	1.0	3	2.9	
Cancer location							
Right	29	28.4	25	24.5	54	52.9	0.12
Left	33	32.4	15	14.7	48	47.1	
Cancer size							
<5 cm	0	0.0	0	0.0	0	0.0	---
≥5 cm	62	60.8	40	39.2	102	100	
Metastatic status							
M0	3	2.9	8	7.8	11	10.8	0.02*[a]
M1a	40	39.2	19	18.6	59	57.8	
M1b	12	11.8	7	6.9	19	18.6	
M1c	7	6.9	6	5.9	13	12.7	
Modifiable risk factors							
Smoking status							
Non-smoker	14	13.7	18	17,6	32	31.4	0.017*
Smoker	12	11.8	10	9.8	22	21.6	
Ex-smoker	36	35.3	12	11.8	48	47.1	
Comorbidities							
No	50	49.0	36	35.3	86	84.2	0.205
Yes	12	11.8	4	3.9	16	15.7	
Nutritional status							
Underweight	46	45.1	30	29.4	76	74.5	0.927
Normoweight	16	15.7	10	9.8	26	25.5	
Overweight	0	0.0	0	0.0	0	0.0	
Obese	0	0.0	0	0.0	0	0.0	
Occupation							
Non-farmer	54	52.9	38	37.3	92	90.2	0.167[a]
Farmer	8	7.8	2	2.0	10	9.8	

Note: *$P \leq 0{,}05$; [a]Fisher's exact test

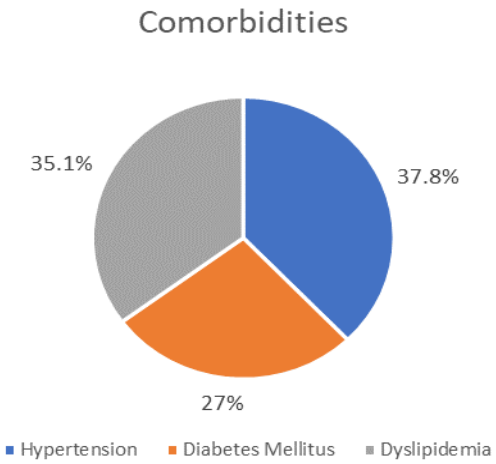

Figure 2. Comorbidities

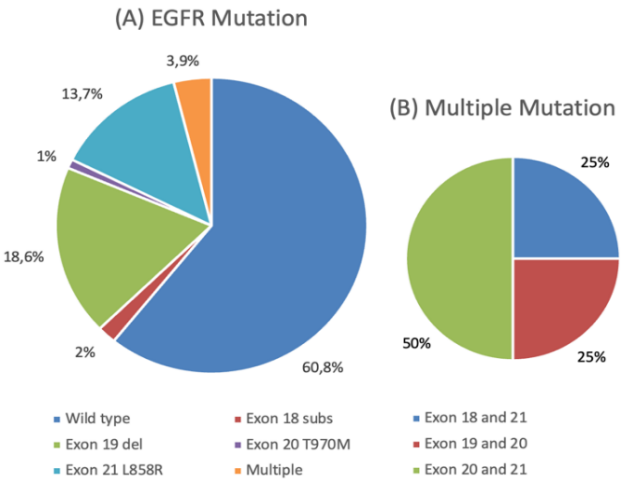

Figure 3. (A) EGFR mutation, (B) Multiple Mutations

The results of the bivariate analysis showed that the statistically significant risk factors with the incidence of EGFR mutations in lung adenocarcinoma patients at Arifin Achmad Hospital were sex, especially male (*P*=0.006), smoking status of ex-smokers (*P*=0.017), and M1a metastases (*P*=0.02). Table 2 shows the relationship between risk factors and the incidence of EGFR mutations in patients with lung adenocarcinoma at Arifin Achmad Hospital.

The logistic regression test aims to obtain odds ratio (OR) and relative risk (RR) values; thus, the dominant risk factors influencing EGFR mutation incidence can be determined. The results showed that the dominant risk factor influencing the incidence of EGFR mutations in patients with lung adenocarcinoma at Arifin Achmad Hospital was ex-smoker status (*P*=0.022; OR=4.3; 95% CI=1.24-15.57), followed by male sex (*P*=0.007; OR=3.409; 95% CI=1.406-8.268), and metastatic status (M1a) (*P*=0.025; OR=0.203; 95% CI=0.05-0.821). Table 3 shows a multivariate analysis of risk factors affecting the incidence rate of EGFR mutations.

Table 3. Multivariate analysis of risk factors influencing the occurrence of EGFR mutations

Variable	OR	95% CI	*P*
Age	1.131	0.404-3.171	0.814
Sex	3.409	1.406-8.268	0.007*
Family history of malignancy	0.769	0.067-8.773	0.833
Cancer location	0.527	0.234-1.187	0.122
Cancer sizes[a]			
Metastatic status	0.203	0.050-0.821	0.025*
Smoking status	4.396	1.241-15.573	0.022*
Comorbidities	0.743	0.234-2.360	0.743
Nutritional status	0.463	0.138-1.552	0.463
Occupation	0.958	0.384-2.391	0.927

Note: *$P \leq 0{,}05$; [a]statistical tests were not carried out because the value was constant

Based on Table 3, smoking status (ex-smokers), followed by sex (male), and metastatic status (M1a) are the dominant risk factors influencing the incidence of EGFR mutations in lung adenocarcinoma patients at Arifin Achmad Hospital. The status of ex-smokers affects the incidence of EGFR mutations by 4.3 times compared to non-smokers and smoking counterparts. Male sex affects the incidence of EGFR mutations by 3.4 times compared to females, while M1a metastatic status affects the incidence of EGFR mutations 0.2 times compared to M1b and M1c.

DISCUSSION

The current technological developments in lung cancer studies towards biomolecular (genetic) aspects make targeted therapy a promising therapeutic option. Overall, EGFR mutations indicate a good prognosis in lung cancer patients with a role for targeted therapy. Epidemiological studies related to the incidence of EGFR mutations showed that EGFR mutations were more common in young patients, non-smokers, and adenocarcinoma types.[18]

A retrospective study conducted at various referral hospitals in Indonesia by Syahruddin et al in Indonesia and Elhidsi et al at Persahabatan Hospital also showed that EGFR mutations were more common in female patients, non-smokers, and Adenocarcinoma types.[19,20] This present study found

that most of the patients with lung adenocarcinoma who had EGFR mutations were male (70.6%), over 45 years old (81.4%), and ex-smokers (47.1%).

The majority of the subjects were in the age group of ≥45 years (81.4%). This result is consistent with a multinational prospective epidemiological study that found the median age of patients from several regions in Asia was 60 years old with a range of 17 to 94 years old.[21] Wu et al in Taiwan found more EGFR mutations in the age group of >50 years than those aged <50 years (84.5%). [22] Xia et al in China, who studied 1472 patients with EGFR mutations, found that only 5% were in the age group of ≤45 years and 95% of patients aged >45 years. [23]

Choi et al in Korea showed that the prevalence of EGFR mutations was found more in older age groups, i.e., the 50-59-year-old group (23.4%), the 60-69-year-old group (29%), and the 70-79 years (31.3%).[24] A central study in Indonesia by Syahruddin et al, a study at Persahabatan Hospital by Elhidsi et al, and a study at Adam Malik Hospital by Soeroso et al found that most subjects were elderly patients. [16,21]

The process of cell DNA mutation occurs throughout life and accumulates at a late age, which contributes to cancer. Most cases of malignancy occur at the age of 50 years and over, with a case prevalence of 90%. The cell aging process (senescence) and cell changes that occur due to exposure to carcinogens in tissues will determine the impact of oncogenic mutations and continue in the process of carcinogenesis. Mutation processes and DNA damage will accumulate at a late age with several risk factors due to biological processes or exposure to other risk factors. The prevalence of lung cancer has been reported to increase in a similar curve in the elderly, both for smokers and non-smokers.[25]

This present study showed that the majority of patients were male (70.6%). This result is similar to a study by Liu et al in China with 148 lung adenocarcinoma patients and showed that there were more male patients than female patients; 57.4% and 42.6%, respectively.[26] Leal et al in Brazil also reported a total of 2544 patients with lung adenocarcinoma, of which 91.6% were male and 8.4% were female.[27] Pi et al in China also reported more male patients than female patients.[28] Zhou et al in China also obtained that the male prevalence was 52.1% and the female prevalence was 45.2%.[29] Furthermore, the Molecular Epidemiology Prospective Study in Asia (PIONEER) pointed out that the prevalence of male sex in adenocarcinoma was 56.6% of cases.[18]

Most of the male patients (70.6%) in this study were having risk factors for ex-smokers and smokers. While the female patients (29.4%) were not smokers and were elderly (>45 years). The dominant occurrence of adenocarcinoma in male patients in this study is thought to be due to the earlier interaction of tobacco-specific nitrosamine (TSNA), which would have an accumulating effect on cell DNA damage; therefore, it would contribute more quickly to the conversion and progression phase of the carcinogenesis process. Meanwhile, the older women subjects in this study are thought to be associated with low estrogen levels (menopause), which supports the process of carcinogenesis.[30]

The results of this study also showed that most patients had no family history of malignancy (97.1%). Kim et al in Korea also reported the prevalence of patients with a small family history of malignancy, i.e., 9% of cases.[31] In contrast to the previous study, Cheng et al in China reported that patients with a family history of malignancy had a higher risk of EGFR mutations.[32] These findings can be attributed mainly to early detection, and surveillance cases of malignancy are still low in Riau province; thus, most patients are not aware of any family history of malignancy.[33]

In this study, most of the lung cancer locations were in the right lung, with a size of ≥5 cm, and having M1a metastatic status (pleural effusion or pericardial effusion, nodules in the pleura or pericardium, or nodules in the contralateral lobe). Epidemiological studies in Asia (PIONEER) reported the incidence of metastases in lung adenocarcinoma patients with EGFR mutations was 27.8% of cases.[18] Calibasi-Kocal et al in Turkey reported the prevalence of right

lung cancer was higher than left lung cancer, i.e., 52.9% and 47.1%, respectively.[34]

The incidence of metastases in this study was reported to be 51.5% of cases. Chen et al in China found that bone metastases (44.1%) had the highest prevalence, followed by pleural metastases (36.1%).[35] Meanwhile, a study in Spain reported that contralateral lung metastases (43%), regional lymph nodes (34.4%) metastases, and pleural effusion (24.8%) were the highest metastases events found in their study subjects.[36]

The predominant location of cancer in the right lung is associated with the anatomy of the right main bronchus which is more sloping than the left main bronchus; thus, the epithelium of the right lung bronchi is more easily exposed to carcinogens. The dominant cancer size of ≥5 cm in this study is thought to be related to inadequate early detection of lung cancer cases. Data from the Riau Provincial Health Office shows that chest radiological support is not evenly distributed in first-level health facilities outside the city of Pekanbaru.[33]

Lung cancer metastases may occur *per continuum* in surrounding tissues, lymphatics, or hematogenous. Lymphatic spread due to the process of lymphangiogenesis through the role of Vascular Endothelial Growth Factor (VEGF) from lung cancer lesions occurs mostly in the hilus and mediastinal lymph nodes (regional lymphatics). Meanwhile, hematogenous spread preceded by the process of neovascularization around the cancerous lesion occurs farther from the cancerous lesion.[43]

The spread of primary tumors to other sites involves several steps consisting of (1) changes and rearrangement of the cytoskeleton, (2) degradation of the extracellular matrix, (3) local invasion, (4) intravasation, (5) transport and survival in the circulatory system, (6) extravasation, and (7) proliferation at a new site.[37,38]

In this present study, the pleura was found to be the most common site of metastases, followed by the pericardium and the contralateral lung. This result follows a study by Elhidsi et al at Persahabatan Hospital.[21] This finding is thought to be associated with adenocarcinoma lesions, which are usually located in the periphery; thus, it is more often reported to have *per continuum* metastatic spread to the pleural organs, causing pleural effusion or nodules. Another metastatic focus of lung adenocarcinoma that has been reported is lymph nodes through the lymphatic system.[39]

The results of this study indicated that the majority of the study subjects did not have comorbidities (84.3%). In contrast to this study, Choi et al in Korea found that most patients were found to have comorbidities, i.e., diabetes and hypertension. A study in Spain also reported the prevalence of comorbidities found in patients, i.e. hypertension (35.5%), chronic obstructive pulmonary disease (24.7%), cardiovascular disease (16.6%), and diabetes (15.4%).[40] This difference could be due to the smaller number of study subjects compared to the comparative studies; therefore, the number of comorbidities found in this study was smaller.

Nutritional status is a risk factor that can determine the survival of patients with malignancy. Cancer cells can increase lipid metabolism, resulting in increased lipid uptake. The nutritional status of patients with malignancy will determine the patient's survival and prognosis. [41,42] Most of the subjects in this study had the nutritional status of underweight (74.5%). In contrast to this study, Chen et al in China reported that norm weight was the most common nutritional status of the study subjects (54%), followed by overweight in 36% of patients, and underweight in 10% of patients.[43]

A study by Jiang et al in America, Europe, and Asia also reported norm weight in 44% of patients, followed by overweight in 34%, obese in 18%, and underweight in 4% of patients.[44] Differences in nutritional status characters in this study and studies abroad are thought to be due to the differences in demographics and cancer stages in the study subjects.

Lung adenocarcinoma patients in this study experienced an unintentional decline in nutritional status influenced by several factors. Generally, the stage and type of cancer are one of the factors that can cause a decrease in nutritional status.[45] In this study, 89.2% of the study subjects were in Stages

IVA and B; thus, it contributed to the dominance of the nutritional status of underweight (74.5%) in this study. Another factor that can cause weight loss and loss of muscle mass is the adipokinetic process, in which the breakdown of lipids in adipose tissue caused by a process of malignancy leads to a decrease in nutritional status.[45,46] Several other factors cause the nutritional status of underweight in most of the subjects in this present study are the side effects of the treatment, the frequency of treatment, and hospital stay, which will interfere with food intake and cause malnutrition in the patients.[47]

Based on smoking status in this study, the prevalence of ex-smokers was higher than smokers and non-smokers, i.e., 47.1%. Zhou et al stated that the prevalence of ex-smokers was higher than the prevalence of smokers, 75.3% and 24.7%, respectively.[48] Jia et al observed that there were more non-smokers than smokers in their study, i.e., 85%.[49] Pi et al discovered that non-smokers were more frequent than smokers in their study, i.e., 55%.[50]

Epidemiological prospective studies in several regions in Asia reported that most of the study subjects were non-smokers, i.e., 52.6% of cases, followed by smokers in 22.1% of cases, and ex-smokers in 20.9% of cases.[18] Leal et al obtained differences from the results of previous studies, i.e., most of their study subjects were smokers (39%), followed by non-smoker subjects (31%), and ex-smokers (30%).[51]

Cigarettes produce oncogenes directly or indirectly from tobacco smoke inhaled directly by smokers or from smoke exhaled by active smokers. In general, the two kinds of smoke produced by burning tobacco affect the development of DNA mutations. Smoking will cause DNA damage through the gradual accumulation of various mutations, i.e., (1) the initiation phase, (2) the promotion phase, (3) the conversion/transformation phase, and then (4) the progression phase. This DNA mutation will result in the transformation of benign progenitor cells in the lungs into neoplastic cells that have malignant properties and possibly develop into metastases. This cancer development results from the growth signal regulation of the lung cancer cells.[52]

Cigarettes can lead to the development of cancer in both smokers and non-smokers. Nicotine smoke inhaled by smokers will cause an accumulation of harmful substances in the lungs. Meanwhile, cigarette smoke, which becomes air pollution, will combine with gases in the air and form oncogene compounds, which will be the cause of the development of lung cancer in non-smokers. This combined compound of cigarette smoke and the air is an aerosol containing about $1x10^{10}$ particles per milliliter, which has the potential to be carcinogenic. Some of the compounds contained polycyclic aromatic hydrocarbons (PAHs), aromatic amines, N-nitrosamines, and other organic or non-organic components, such as benzene, vinyl chloride, arsenic, and chromium.[53]

Based on the International Agency for Research on Cancer (IARC), tobacco smoke has approximately 50 carcinogens. The TSNA is the main substance associated with the development of lung cancer formed by the nitrosation of nicotine during tobacco processing. The TSNA that is reported to cause lung adenocarcinoma is 4-(methylnitrosamino)-1-(pyridyl)-1-butanone (NNK). DNA mutations that result in the activation of the KRAS and EGFR oncogenes have been reported to be associated with NNK.[53]

Most of the study subjects of this present study were non-farmers (90.2%), whereas farmers accounted for 9.8% of all study subjects. Occupation is one of the environmental factors known to have a relationship with the pathogenesis of lung cancer. Zhou et al reported the occurrence of EGFR mutations associated with the work of patients, especially farmers.[54] Riza et al reported a case study of a 70-year-old male patient who worked as a farmer with an EGFR mutation. Sun exposure was one of the factors for the development of EGFR mutations in this patient.[55] The difference in the results of this study with previous comparative studies can be caused by factors of demographic and social differences in the people of Riau Province.

The highest status of EGFR mutations in this study was wild type (60.8%), followed by exon 19 del (18.6%), and exon 21 subs (13.7%). Liu et al in China showed that based on EGFR mutation status, the wild type was more frequent in their study (49% of all cases), followed by exon 19 in 30% of cases, and exon 21 in 21% of cases.[56] Leal et al in Brazil stated that the wild type was more frequent in their study (77.3%), followed by mutations in exons 19 and 21 in 22.7% of all cases.[51] Leduc et al in France found that the percentage of EGFR mutations was 51% in exon 19, 38% in exon 21, 5.5% in exon 18, and 5.5% in exon 20.[57]

A meta-analysis of 456 studies reported 30,466 patients with EGFR mutations and found that mutations in exon 19 were more frequent in 343 studies, or 16.7% of cases, followed by mutations in exon 21 in 330 studies, or 12.3% of all cases.[58] The findings of this present study are in accordance with previous studies with wild type as the most common genotype in patients with lung adenocarcinoma, and the most common EGFR mutations are found in exon 19 del and 21 subs (common mutation), followed by exon 18 subs and exon 20 ins (uncommon mutation).

Based on the results of this study, it was found that the male sex had a significant relationship with the incidence of EGFR mutations (P=0.006). Various studies in China, such as by Mei et al, reported that sex was associated with the incidence of EGFR mutations (P=0.0001).[59] Jia et al identified the sex of 503 patients with lung adenocarcinoma and found a statistically significant association with the incidence of EGFR mutations (P<0.0001).[60] Hong et al pointed out that sex was a risk factor associated with EGFR mutations (P=0.007).[61] Wang et al also observed that sex characteristics in their cohort study were associated with EGFR mutations (P<0.001).[62]

In general, correlative analysis studies in Asia show that females have a statistically significant relationship with EGFR mutations, different from those in Europe and America because it is associated with race and ethnicity. The prospective epidemiological study in Asia (PIONEER) reported that females had a statistically significant relationship with the incidence of EGFR mutations.[18] Leal et al in Brazil discovered that female was statistically associated with the incidence of EGFR mutations (P<0.0001).[51] Zhou et al in China also reported a statistically significant association of the female sex with EGFR mutations (P<0.001).[48] Choi et al in Korea also reported a statistically significant relationship between the female sex and the incidence of EGFR mutations (P=0.007).[63] Sahoo et al in India also obtained that exon 18 and 19 EGFR mutations had a statistically significant association with sex, especially with females.[64]

EGFR mutations are generally found to be higher in women in the Asia Pacific population. Some hypotheses stated that this is related to the level of the estrogen hormone in women, which affects the polymorphism of the EGFR structure, thus it is more likely to mutate. The findings of this present study, which are contradictory to several previous studies, are due, among other things, to differences in the distribution of the study subjects. The findings of non-homogeneous sex study subjects (70.6% male and 29.4% female) may affect the results of the analysis of the association with the incidence of EGFR mutations in this present study.[65]

In addition, the finding of male sex in this study follows a meta-analysis study reported by Benbrahim et al, which analyzed more broadly the populations of several countries in Asia, the Middle East, and Africa. Benbrahim et al stated that the overall male sex ratio was 2.15 higher than that of the female counterparts and was significantly associated with the incidence of EGFR mutations.[65]

Smoker status, especially ex-smokers, in this present study, showed a statistically significant relationship with the mutation rate (P=0.017). These results are found to be different from previous studies, such as epidemiological studies of EGFR mutations in Asia, which reported that non-smokers had a significant association with the incidence of EGFR mutations.[18]

Mei et al found that the smoking status in 296 adenocarcinoma patients had a statistically significant relationship with the incidence of EGFR mutations (P=0.0001).[66] Jia et al, reported that non-smoker status had a statistically significant

association with the incidence of EGFR mutations (*P*<0.0001).[60] Furthermore, Hong et al also obtained that non-smokers had a statistically significant association with the incidence of EGFR mutations (*P*=0.003).[67]

A study in Brazil reported that smoking status, especially non-smokers, had a statistically significant association with the occurrence of mutations (*P*<0.0001). Pi et al in China also reported that smoking status, especially non-smokers, was significantly associated with the incidence of EGFR mutations (*P*<0.001).[50] Zhou et al in China also stated that smoking status was associated with the occurrence of mutations (*P*=0.003), especially in ex-smokers.[48] Tseng et al reported a statistically significant relationship between smoking and the incidence of EGFR mutations in lung cancer patients. A similar result was also obtained by Russo et al in Italy who reported the association of smoking status with the incidence of EGFR mutations, especially among ex-smokers (*P*=0.002).[68]

This present study showed that the smoker status of ex-smokers was associated with the incidence of EGFR mutations. Patients who were smokers had a lower incidence of EGFR mutations. Nonetheless, patients with EGFR mutations and who were smokers have poorer survival rates and prognosis compared to their non-smoker counterparts.[69]

Smoking is the main risk factor associated with the mutation process that can cause lung cancer. Smoking can destroy bronchial epithelial structures which will cause cell apoptosis. Bronchial epithelium that undergoes apoptosis and is exacerbated by other risk factors will increase the incidence of lung cancer by 54.7%.[70]

Based on the literature from Oncotarget, the level of DNA addition is inversely related to age and the initiation of smoking (ex-smokers). Patients with a history of smoking from a young age (ex-smokers) are more susceptible to DNA damage. Meanwhile, patients who start smoking at an older age have less risk of DNA damage. Furthermore, damage to cell DNA can potentially mutate the EGFR gene.[71] This could explain why the incidence of EGFR mutations is related to the status of ex-smokers in this present study.

It is known that M1a metastatic status in this present study had a statistically significant relationship with the mutation rate (*P*=0.02). Russo et al in Italy reported that the characteristics of EGFR mutations influenced the incidence of cancer mutation development.[72] Li et al in China also found that EGFR mutations were statistically associated with the incidence of cancer metastases.[73]

Furthermore, Guan et al in China also discovered that the incidence of EGFR mutations was statistically related to tumor size and TNM stage (*P*<0.001). One of the important predictors related to the incidence of metastases was EGFR mutation, especially brain metastases.[73] Patients with metastases were much more frequently reported to have EGFR mutations than patients who did not have metastatic events. Some of the most reported cases of metastases were metastases to the bones and the brain.[74]

It was observed that the male sex, M1a metastatic status, and ex-smoker status were the dominant risk factors that affect the incidence of EGFR mutations in patients with lung adenocarcinoma at Arifin Achmad General Hospital. Ex-smoker status affects EGFR mutations by 4.3 times compared to smokers and non-smokers. The male sex affects EGFR mutations by 3.4 times compared to the female sex. Furthermore, M1a metastatic status affects EGFR mutations by 0.2 times compared to M1b and M1c.

Several studies explain that sex and individual smoking status are associated with the incidence of EGFR mutations. Male patients who do not smoke have an EGFR mutation frequency 19 times higher than their smoker counterparts. The incidence of EGFR mutations increased 2-fold higher in the group of female patients who don't smoke compared to their smoker counterparts, women who smoke. Based on the sex of non-smokers, EGFR mutations are 2.2 times lower in male patients.[75]

Sahoo et al reported that the female sex had a 1.5 times higher risk than the male to have EGFR mutations.[76] Kit et al conducted a multivariate test of

risk factors with the incidence of EGFR mutations, one of which was smoking status, which showed that the incidence of mutations was increased in non-smokers (OR=4.31; 95% CI=2.75-6.75; *P*<0.0001) compared to smokers. This study also stated that women were 4.5 times more likely to have EGFR mutations.[77]

A study in Spain analyzed the factors associated with the occurrence of EGFR mutations. Based on the multivariate analysis of this study, the independent factors that were reported to be associated with the incidence of EGFR mutations were sex, smoking status, and some secondary lesions. Women in this study were reported to have a 2 times higher risk of developing EGFR mutations than men. The smoking status of patients was divided into non-smokers, ex-smokers, and smokers. Ex-smokers had a 2.2-fold risk of developing EGFR mutations.[40]

Several studies have reported that EGFR mutations are not significantly associated with smoking. However, one study reported that former/ex-smokers who had quit smoking more than 1 year before diagnosis had an increased risk of possible EGFR mutations. Female sex was a significant risk factor affecting EGFR mutations regardless of the patient's smoking status. EGFR mutation is an independent factor in the development of metastases in patients, especially brain metastases. Han et al also stated that EGFR mutations could increase the incidence of metastases. Based on the multivariate test, the study also reported that EGFR mutations were associated with brain metastases (*P*=0.022; OR 2.515; 95% CI=1.142-5.542). [78,79]

LIMITATIONS

This study has several limitations. First, this study only involved one center, therefore, the results of this study cannot be generalized to general-wider populations. Further multicentered studies with a bigger sample and a longer study duration are needed.

CONCLUSION

The risk factors for ex-smokers affect the incidence of EGFR mutations by 4.3 times compared to their non-smoker and smoker counterparts. The male sex affects the incidence of EGFR mutations by 3.4 times compared to the female sex. The M1a metastatic status affects the incidence of EGFR mutations by 0.2 times compared to M1b and M1c. Male, ex-smokers, and metastatic status (M1a) are the dominant risk factors that affect the incidence of EGFR mutations in lung adenocarcinoma patients at Arifin Achmad Hospital.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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