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PREVALENCE OF ALK (D5F3) EXPRESSION IN NON-SMALL CELL LUNG CANCER IN MRCCC SILOAM HOSPITALS

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ABSTRACT

Background: Lung cancer is the primary cause of cancer-related illness and death worldwide. GLOBOCAN 2022 reports 2,480,675 lung cancer cases (12.4% of all cancers), with the highest mortality rate (1,817,469 deaths). ALK rearrangement plays a significant role in tumor progression, survival, and metastasis, but the prevalence of ALK-positive tumors varies across populations. Data on ALK rearrangement in multi-ethnic populations like Indonesia remains limited. **Objective:** To describe the prevalence and distribution of ALK rearrangement in Indonesian NSCLC patients by gender, age, and histological subtype. **Methods:** This descriptive study uses a cross-sectional design with a retrospective approach based on the results of immunohistochemistry of ALK (D5F3) expression in NSCLC patients. This study included all patients diagnosed with NSCLC who were examined for ALK (D5F3) expression. The exclusion criteria of this study were patients with incomplete data, patients diagnosed with anaplastic large cell lymphoma, and lung metastasis. **Results:** The prevalence of ALK-positive NSCLC patients at MRCCC Siloam Hospitals Semanggi from 2020 to 2024 was 24 cases (7.8%) out of a total sample of 306. Most cases were male patients, accounting for 14 cases (58.3%). ALK-positive cases were predominantly found in patients aged 60 years and under, accounting for 14 cases (58.3%). Lung adenocarcinoma is the NSCLC subtype that has the highest number of ALK-positive cases, with 21 cases (87.5%). **Conclusion:** This study reveals a higher prevalence of ALK-positive NSCLC in the Indonesian population. This result provides a treatment option for NSCLC patients who have negative expressions of EGFR and PD-L1, offering them new hope for targeted therapy.

INTRODUCTION

GLOBOCAN 2022 states that lung cancer continues to be the primary cause of cancer-related death globally, accounting for 2.48 million new cases each year, or 12.4% of all cancer diagnoses. The disease accounts for a staggering 1.82 million deaths each year, constituting 18.7% of total cancer mortality.[1] This worldwide burden is particularly noticeable in Indonesia, where 38,904 cases (9.5% of all cancers) of lung cancer have been reported, making it the second-most prevalent malignancy, following breast cancer. The gender disparity is striking, with males accounting for 29,107 cases (15.4% of male cancers) compared to 9,797 cases (4.4% of female cancers) in women. Most alarmingly, lung cancer claims 34,339 Indonesian lives annually, representing 14.1% of the nation's cancer deaths (242,988 total cancer-related mortality).[2]

About 85% of all incidences of lung cancer are non-small cell lung cancer (NSCLC), with small cell lung cancer accounting for the remaining 15%. NSCLC is further classified into three major histological subtypes: adenocarcinoma (the most common), squamous cell carcinoma, and large cell carcinoma.[3] Adenocarcinoma demonstrates a unique epidemiological profile, showing higher prevalence among non-smokers and women, suggesting alternative etiological factors beyond active tobacco

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use.[4] These include exposure to secondhand smoke (SHS), which contains over 70 known carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and benzopyrene, as well as environmental pollutants from biomass fuel combustion.[5]

The molecular landscape of NSCLC has become increasingly crucial in therapeutic decision-making. Anaplastic lymphoma kinase (ALK) gene rearrangements have become an essential therapeutic target among various driving mutations. ALK, a tyrosine kinase receptor, has been shown to play a significant role in the development of NSCLC. However, chromosomal rearrangements—most commonly the EML4-ALK fusion—result in constitutive kinase activity that promotes oncogenesis by activating downstream pathways, such as the RAS-ERK, JAK-STAT, and PI3K/AKT pathways. These alterations lead to uncontrolled cellular proliferation, survival, and metastasis.[6]

Globally, ALK rearrangements occur in approximately 4% of NSCLC cases, but demonstrate significant ethnic variation: 3% in Indian populations, 5% in East Asians, and 7% in Caucasians. Since there has been a notable response to ALK tyrosine kinase inhibitors (TKIs), including crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib, these mutations are clinically relevant.[7] ALK-positive NSCLC exhibits distinct clinicopathological characteristics, typically in younger patients, light or never-smokers, and those with adenocarcinoma histology, particularly tumors showing acinar or solid growth patterns.[8]

Therefore, accurate identification of ALK rearrangements is essential for optimal patient care. The VENTANA anti-ALK (D5F3) Rabbit Monoclonal Primary Antibody can be used in immunohistochemistry (IHC) to detect ALK rearrangements. ALK-positive tumour cells show an intense granular cytoplasmic staining as a typical staining pattern. Comprehensive histopathological evaluations and IHC enable precise tumor classification and molecular characterization, forming the foundation for personalized treatment strategies.[9]

Despite these advances, ALK testing remains underutilized in many resource-limited settings, including Indonesia. This gap in molecular diagnostics is particularly concerning, given the availability of effective targeted therapies and the country's unique genetic diversity across its numerous ethnic groups. This study at MRCCC Siloam Hospitals aims to determine the frequency of ALK (D5F3) expression in patients with non-small cell lung cancer and to investigate its distribution across patient characteristics, including age, gender, and NSCLC subtypes. The findings will provide valuable insights for optimizing diagnostic protocols and therapeutic decision-making in Indonesia's diverse population.

The clinical implications of this research are significant because targeted treatments have demonstrated better performance and tolerance compared to traditional chemotherapy for ALK-positive patients.[10] Furthermore, establishing local epidemiological data will inform stakeholders and provide them with suggestions, enabling them to allocate resources for molecular testing in Indonesia. As precision oncology continues to advance, studies like this will be increasingly important in ensuring equitable access to molecular diagnostics and targeted therapies across diverse healthcare settings.

METHODS

This descriptive study employs a cross-sectional study design. The study utilizes secondary data, collected through a retrospective approach, based on ALK (D5F3) immunohistochemistry results from NSCLC patients in the Anatomical Pathology laboratory of MRCCC Siloam Hospitals Semanggi, from 2020 to 2024. We collect data on age, gender, NSCLC subtypes, and ALK expression status, which is recorded in the form. The sampling method is total sampling, which includes all patients who meet the inclusion and exclusion criteria. The inclusion criteria for this study were all patients diagnosed with NSCLC who were examined for ALK (D5F3) expression. The exclusion criteria of this study were patients with incomplete data, patients diagnosed with anaplastic large cell lymphoma, and individuals with metastatic cancer originating from other organs and spreading to the lung. The data were processed using descriptive statistics in the IBM SPSS Statistics 26 application and presented in a tabular format.

RESULTS

This study examined 306 NSCLC patients who underwent ALK expression analysis at MRCCC Siloam Hospitals Semanggi between 2020 and 2024.

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Sample Characteristics

The youngest patient in this study was 27 years old, while the oldest patient was 90 years old. The average age of patients was 60.91 ± 11.74 years. NSCLC samples were found more frequently in patients aged over 60 years, with 173 cases (56.6%), compared to patients aged ≤ 60 years, with 133 cases (43.4%). NSCLC patients were more likely to be male, with 183 patients (59.8%), than female, with 123 patients (40.2%). Lung adenocarcinoma is the most prevalent subtype of NSCLC, accounting for 254 cases (83%), followed by lung squamous cell carcinoma, which has 51 cases (16.7%), and lung large cell carcinoma, which has just one case (0.3%). In this study, we found 24 cases (7.8%) of ALK-positive and 282 cases (92.2%) of ALK-negative NSCLC patients. This can be seen in Table 1.

Table 1. Sample Characteristics

Characteristics	Frequency (n)	Percentage (%)
Total	**306**	**100%**
Sex		
Male	183	59.8%
Female	123	40.2%
Age (years)		
≤ 60	133	43.4%
> 60	173	56.6%
Mean ± SD	60,91 ± 11,74	
Range	27-90	
NSCLC Subtype		
Adenocarcinoma	254	83%
Squamous cell carcinoma	51	16.7%
Large cell carcinoma	1	0.3%
ALK (D5F3) Expression		
ALK+	24	7.8%
ALK−	282	92.2%

ALK-positive was more common in male patients, with 14 cases (58.3%) in males and 10 cases (41.7%) in females. ALK-positive NSCLC patients ranged in age from 28 to 77 years old, with an average of 54.25 ± 14.46 years. NSCLC patients with ALK-negative tumours have a higher average age (61.47 ± 11.33 years) compared to those with ALK-positive tumours.

NSCLC patients diagnosed as ALK-positive were more likely to be younger, specifically ≤ 60 years old, with 14 cases (58.3%), compared to those over 60 years old, with 10 cases (41.7%). ALK-positive NSCLC was contributed mainly by lung adenocarcinoma subtype with 21 cases (87.5%), followed by lung squamous cell carcinoma with 3 cases (12.5%). There were no ALK-positive cases in the large cell lung carcinoma subtype. This can be seen in Table 2.

Table 2. Distribution of Patients' Sex, Age, and NSCLC Subtype Based on ALK (D5F3) Expression Outcomes

	ALK+ (n = 24)	ALK− (n = 282)	Total (n = 306)
Sex			
Male	14 (58.3%)	169 (59.9%)	183 (59.8%)
Female	10 (41.7%)	113 (40.1%)	123 (40.2%)
Age (years)			
≤ 60	14 (58.3%)	119 (42.2%)	133 (43.4%)
> 60	10 (41.7%)	163 (57.8%)	173 (56.6%)
Mean ± SD	54.25 ± 14.46	61.47 ± 11.33	60.91 ± 11.74
Range	28-77	27-90	27-90

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NSCLC Subtype			
Adenocarcinoma	21 (87.5%)	233 (82.6%)	254 (83%)
Squamous cell carcinoma	3 (12.5%)	48 (17%)	51 (16.7%)
Large cell carcinoma	0 (0%)	1 (0.4%)	1 (0.3%)

DISCUSSION

According to GLOBOCAN statistics, lung cancer is the most frequent cancer with a high mortality rate. The development of molecular biology has created new therapeutic methods for lung cancer, mainly targeted therapy for advanced lung cancer that cannot be treated with surgery or chemotherapy. Screening for targetable mutations such as ALK is essential to determine the appropriate target and treatment for patients with NSCLC. This can help increase the success rate of therapy and improve patients' prognosis and life expectancy.

Men are more likely than women to develop lung cancer because of their smoking habits, therefore increasing the incidence and mortality rate of lung cancer in male patients. At the same time, non-smoking female patients tend to suffer from lung adenocarcinoma.[11] The main findings showed that the distribution of patients by gender was dominated by 183 males (59.8%), compared to 123 females (40.2%). This gender distribution pattern is in line with the report by Bray *et al*. (2022), which shows the ratio of global lung cancer incidence between men and women is around 2:1.[12]

National data from Hanafi *et al.* (2024) reinforced this finding by showing that 454 people (64.2%) of lung cancer patients in Indonesia were male.[13] Bruno *et al.* (2024) also found a similar proportion, with 657 (58.6%) male patients and 465 (41.4%) female patients.[14] However, interesting results were found in the studies of Hou et al. (2023) and Mok et al. (2021), which revealed a higher proportion of female patients with lung cancer, accounting for 378 (54.46%) and 171 (56.43%) individuals, respectively.[15,16] This phenomenon of changing gender trends is explained by the studies of Gee *et al*. (2024) as the impact of the transformation of global smoking patterns, where there has been a significant decline in smoking habits in males since the 1960s accompanied by an increase in smoking prevalence in females, thus fundamentally changing the epidemiological landscape of lung cancer in recent decades.[17]

The study found that the average age at diagnosis was 60.91 years, with a standard deviation of ±11.74 years, ranging from 27 to 90 years. A total of 173 patients (56.6%) of cases occurred in the age group above 60 years, indicating that NSCLC predominantly affects the elderly population. This finding has high consistency with various international studies, including Liu *et al.* (2022) in China, who reported a mean age of diagnosis of 61.92 ± 10.24 years with a range of 27-87 years,[18] Heriyanto *et al.* (2020) reported a similar finding in Indonesia, with an average age of 63.5 years (ranging from 41 to 82 years).[19] Similar patterns are also observed in the research of Hou et al. (2023), who found that 357 (51.44%) of 694 patients aged over 60 years.[15], Xia *et al.* (2021) with 3704 (56.32%) of 6576 patients[20], Liu et al. (2022) reported that 269 (59.4%) of 453 NSCLC patients were elderly.[18]

However, there are interesting variations in data from Bruno et *al.* (2024) in Italy, Lin *et al.* (2023) in the US, and de la Rosa *et al.* (2022) in Spain, who reported older ages of diagnosis, 71 years, 69 years, and 65.5 years, respectively.[14,21,22], indicating differences in patient demographic characteristics between certain geographic regions and ethnic groups.

In this study, histopathological investigation indicated that adenocarcinoma was the most common NSCLC subtype in 254 cases (83%), followed by squamous cell carcinoma in 51 instances (16.7%), and giant cell carcinoma in only 1 case (0.3%). This distribution pattern shows striking agreement with recent international studies. A study by Liu et al. (2022) in China identified 341 cases of adenocarcinoma (75.3%) and 106 cases of squamous cell carcinoma (23.4%) among a total of 453 cases.[18]. while Xia *et al*. (2022) reported 4897 (74.5%) adenocarcinoma cases and 982 (14.9%) squamous cell carcinoma cases from an analysis of 6,576 cases.[20] Data from Spain, as studied by de la Rosa et al. (2022), also showed a similar pattern, with 458 (81%) cases of adenocarcinoma, 71 (12.7%) cases of

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squamous cell carcinoma, and 19 (3.4%) cases of large cell carcinoma among 559 cases studied.[22]

This epidemiological transformation in histological subtype patterns was explained by the study by Gee *et al.* (2024) due to the evolution of smoking habits and advancements in modern cigarette technology. The decrease in the incidence of squamous cell carcinoma correlates strongly with the decline in male smoking prevalence since the late 1960s. At the same time, the increase in adenocarcinoma is linked to modifications in cigarette filter design that allow smaller tobacco particles to reach the distal regions of the lungs. These fundamental changes have led to an epidemiological transition where adenocarcinoma emerged as the dominant subtype since 1994 and continues to persist in the contemporary era.[17]

Immunohistochemical analysis in this study of ALK expression revealed 24 (7.8%) ALK-positive cases out of 306, and 282 (92.2%) ALK-negative cases, a finding that falls within the spectrum of global variation. Some studies in Asia reported a higher prevalence of ALK positivity, such as Hou *et al.* (2023), with 65 (9.3%) out of 694 cases in China[15], Liu *et al*. (2022) found 41 (9%) out of 453 cases[18], and surprisingly, Zhang *et al.* (2022) reported a very high rate of 39 (35.77%) ALK-positive out of 109 cases in Tianjin, China[23].

In contrast, studies in other regions showed lower prevalence of ALK-positive, such as the study by Lin *et al.* (2023) that showed 1,042 (2,83%) out of 36,691 cases, study by de la Rosa *et al.* (2022) that showed 16 (5.92%) out of 270 cases, and study by Xia *et al*. (2021) that showed 343 (5.21%) out of 6,576 cases.[20–22] The large-scale research by Allen *et al*. (2021) in the US population provided an interesting epidemiological picture with an overall prevalence of ALK positivity of 519 patients (2.6%) out of 19,895 cases. Still, stratification analysis by race revealed significant disparities. Patients of Asian descent showed the highest prevalence of ALK positivity of 6.3% despite only accounting for 3.1% of the total sample. In comparison, the Caucasian population had a lower prevalence of ALK positivity, ranging from 2.1% to 2.6%.[24] The South region of the US has the lowest prevalence of ALK-positive NSCLC at 154 (1,9%) out of 7,988 cases, while the West region has the highest prevalence, at 108 (3.4%) out of 3,143 cases.[24]. This finding further strengthens the evidence that ALK rearrangements have unique demographic distribution characteristics, with a tendency to occur more frequently in younger patients, non-smokers, and especially in individuals of Asian descent. This biomedical fact has significant clinical implications for the management of NSCLC in Indonesia and the Asian region in general.

Changes in gender-related epidemiological patterns demand awareness of the evolving dynamics of lung cancer patient characteristics. The dominance of the age group over 60 years (56.6%) emphasizes the importance of effective screening mechanisms for the elderly population. Meanwhile, the predominance of adenocarcinoma as the primary histologic subtype, at 83%, requires a precise diagnostic approach. The most clinically relevant aspect is the finding of a prevalence of ALK-positive of 7.8% in the study population, a statistically and clinically significant figure. This finding, together with the evidence that Asian patients tend to have a higher prevalence of ALK-positive (6.3% in the study by Allen *et al*. compared to 2.1-2.6% in other populations), strongly supports the need for routine screening of ALK rearrangement status as an integral component of NSCLC management in Indonesia.

The implementation of targeted therapy, particularly ALK inhibitors in patients with ALK-positive tumors, is an increasingly relevant strategy, complemented by the broader availability of various targeted drugs in the Indonesian pharmaceutical market. The data of this study collectively not only enrich the medical knowledge on the characteristics of NSCLC in Indonesia with the findings of male-dominated gender distribution (59.8%), mean age of diagnosis of 60.91 years, primary histological subtype of adenocarcinoma (83%), and prevalence of ALK-positive of 7.8%, but also provide a strong scientific basis for a precision medicine approach that considers the specific characteristics of the Asian population in the management of NSCLC. Given its high frequency and the established efficacy of targeted therapy, identifying ALK rearrangement status should be considered a standard diagnostic method to enhance clinical outcomes for NSCLC patients in Indonesia.

This study shows essential information about the features of ALK-positive non-small cell lung cancer (NSCLC) patients at MRCCC Siloam Hospitals Semanggi. Gender distribution showed a predominance of male patients, 14 (58.3%) out of 24

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cases, compared to females with 10 cases (41.7%), a pattern consistent with the study by Jahanzeb *et al.* (2021) and the study by Li *et al.* (2021), which reported 51.8% and 54.2% of ALK-positive cases in males, respectively.[25,26]

However, there is an interesting disparity with the results of Lin *et al.* (2023), Hou *et al.* (2023), and Xia *et al.* (2021), who found more female patients with ALK-positive (50.2%, 55.4%, and 51.6% respectively), indicating possible variations in gender distribution based on geographical or ethnic factors.[15,20,21] Age group analysis revealed that 14 cases (58.3%) of ALK-positive patients were ≤ 60 years old and 10 cases (41.7%) were over 60 years old, with the mean age of ALK-positive patients being significantly younger (54.25 ± 14.46 years) than ALK-negative patients (61.47 ± 11.33 years). This finding aligns with previous studies, including Liu et al. (2022), which reported that 30 patients (73.2%) of ALK-positive patients were ≤ 60 years old, with an average age of 55.49 ± 12.62 years.[18] Hou *et al*. (2023) with 41 patients (63.1%) of ≤ 60 years old (mean 55.86 ± 9.41 years),[15] and Zhang *et al* (2022) with a mean age of 56.00 ± 11.13 years.[23] Collectively, we are strengthening the evidence that ALK rearrangements are more frequent in younger populations.

From a histopathological perspective, this study found an absolute predominance of adenocarcinoma as the primary ALK-positive associated subtype (21 (87.5%) out of 24 cases), followed by squamous cell carcinoma (3 (12.5%) cases, without a single ALK-positive case in large cell carcinoma. This pattern is highly consistent with the global literature, with Li *et al*. (2021) reporting 81 (84.4%) cases of adenocarcinoma out of 96 ALK-positive cases,[26] Liu *et al.* (2022) found 37 (90.2%) cases of adenocarcinoma out of 41 ALK-positive cases,[18] Xia *et al.* (2021) recorded 311 (90.7%) cases of adenocarcinoma out of 343 ALK-positive cases,[20] and Hou *et al*. (2023) even reported 100% of 65 ALK-positive cases as adenocarcinoma.[15]

Although the prevalence of ALK-positive squamous cell carcinoma was lower, it was still clinically significant, with 9.4% (study by Li *et al.* in 2021), 9.8% (study by Liu *et al.* in 2022), and 2% (study by Xia *et al.* in 2021),[18,20,26] suggesting that ALK rearrangement screening may still need to be considered in specific non-adenocarcinoma subtypes. This finding is further supported by the report of several ALK-positive cases in rare histological variants in the study by Xia et al. (2021), including adenosquamous carcinoma and neuroendocrine large cell carcinoma, albeit with a low incidence.[20]

The clinical implications of this study are multidimensional. The demographic profile of ALK-positive patients, who tend to be younger with a predominance of adenocarcinoma, may be an essential guide in patient selection for ALK rearrangement testing, given the relatively high cost of molecular testing. An understanding of the histopathological distribution of ALK rearrangement supports a more targeted approach to screening, especially for lung adenocarcinoma. The variation in ALK results between studies highlights the importance of considering geographical factors, such as those in the US, Italy, Spain, and China[14,15,22,24], as well as ethnic factors, such as White, Black or African American, and Asian patients.[21,24] These findings strengthen the scientific basis for the application of ALK inhibitor targeted therapy, which has been shown to provide better outcomes in patients with ALK-positive.

Several factors may influence the variation in results between studies, including differences in rearrangement detection methods (FISH vs IHC vs NGS), patient inclusion criteria, and specific population characteristics. Overall, the findings of this study not only contribute to a more comprehensive understanding of the profile of NSCLC patients with ALK-positive in Indonesia, but also serve as an excellent basis for the future development of more precise diagnostic and therapeutic protocols, confirming the importance of a personalized medicine approach in the management of lung cancer in this modern era.

The limitations of this study include incomplete data on smoking status, TNM staging of NSCLC, and metastasis, as it is not possible to determine the effects of these factors on the outcome of ALK expression.

CONCLUSION

The study shows that ALK rearrangement screening can also provide hope for patients with other subtypes of NSCLC, not just adenocarcinoma. ALK rearrangement is one of the biomarkers to check before starting targeted therapy in NSCLC patients, especially in Asian regions such as Indonesia. ALK

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rearrangement testing can offer therapeutic hope for NSCLC patients with negative EGFR and PD-L1 mutations, as ALK biomarkers provide new options for targeted therapy. Patients with ALK-positive can receive treatments such as Crizotinib, Alectinib, or Nivolumab. This is likely to improve the prognosis and success rate of treatment, thereby extending the life expectancy of patients with advanced NSCLC. Increasing the number of hospitals and labs offering ALK rearrangement testing services is expected to lead to improved targeted therapy for NSCLC. Future research should examine clinical outcomes and the effects of treatment on ALK-positive NSCLC patients who received ALK inhibitors.

ETHICAL APPROVAL

This study received ethical clearance from the Health Research Ethics Commission (KEPK), Faculty of Medicine, Tarumanagara University, with ethical clearance No.510/KEPK/FK UNTAR/XII/2024, also with the approval and consideration of the MRCCC Siloam Hospitals Semanggi in Jakarta.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest in this study.

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AUTHOR CONTRIBUTIONS

The following contributions by the authors: conceptualization, SS and KJS; methodology, SS and KJS; software, KJS; validation, SS; formal analysis, SS and KJS; investigation, KJS; resources, SS and KJS; data curation, SS and KJS; writing-original draft preparation, SS and KJS; writing-review and editing, SS and KJS; visualization, KJS; supervision, SS; project administration, SS and KJS; funding acquisition, SS and KJS.

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