ORIGINAL ARTICLE

Anaplastic Lymphoma Kinase (ALK) Rearrangement of Lung Adenocarcinoma among North Sumatera Population

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ARTICLE INFO

Article history:
Received 1 November 2024
Received in revised form
11 December 2024
Accepted 24 December 2024
Available online 30 January 2025

Keywords:
Adenocarcinoma,
Anaplastic lymphoma kinase,
Cancer,
Lung cancer,
Non-small cell lung cancer.

Cite this as:
Putra MYA Soeroso NN, Afiani D, *et al*. Anaplastic Lymphoma Kinase (ALK) Rearrangement of Lung Adenocarcinoma among North Sumatera Population. *J Respi* 2025; 11: 47-53.

ABSTRACT

Introduction: Lung cancer is a malignancy of the lung parenchyma or bronchi. Globally, cases and deaths of lung cancer continue to increase. Lung cancer remains the most common cancer diagnosis in males. Molecular targeted therapy directed at oncogene driver mutations, such as ALK, improves the prognosis of patients with NSCLC. This study aims to determine the characteristics of lung adenocarcinoma patients and the prevalence of ALK rearrangement among the North Sumatra population.
Methods: This is a descriptive study using data from patient's FFPE ALK examination results and medical records. The laboratory will analyze the patient's FFPE for ALK fusion protein expression using the VENTANA anti-ALK (D5F3) procedure to determine the prevalence of ALK rearrangement.
Results: Of the 34 subjects, it was revealed that the characteristics of lung adenocarcinoma patients were 18 patients aged >60 years (52.9%), male gender 26 patients (76.4%), and heavy smokers 24 patients (70.6%). Based on the pTNM stage, most samples were classified as Stage IVA, with 24 cases (70.6%) showing the highest incidence of metastases to the pleura. There were 2 cases of ALK mutations obtained through immunohistochemical examination with a percentage of 5.8%.
Conclusion: There are relatively few ALK rearrangement mutations in lung adenocarcinoma patients without screening. Additional research is needed to ascertain the distribution of lung adenocarcinoma patient characteristics associated with a higher prevalence of ALK rearrangement mutations.

INTRODUCTION

Lung cancer is a malignancy or tumor originating from the lung parenchyma or within the bronchi. Globally, lung cancer cases and deaths continue to increase. Lung cancer has been the most frequently diagnosed cancer for decades. Lung cancer remains the most common cancer diagnosis in men, with an estimated 1.37 million people diagnosed in 2018[1].

Lung cancer can be divided into two major types, namely non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). The most common type of lung cancer is NSCLC, around 85% of all lung cancers. NSCLC consists of several subtypes, including squamous cell carcinoma (epidermoid carcinoma) at 20%, adenocarcinoma at 38.5%, and large cell carcinoma at 2.9%. Meanwhile, SCLC is the highest malignant tumor originating from cells that have neuroendocrine-like characteristics and accounts for 15% of lung cancer cases[2,3].

Recent research on molecular targeted therapy directed at driver oncogene mutations, such as Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), ROS1, RET1, NTRK1, and KRAS improves the prognosis of patients with NSCLC. Research in Indonesia shows a high proportion of EGFR mutations in lung adenocarcinoma, reaching 44% and KRAS mutations were not found in the North Sumatra population. Currently, there is no data on ALK in North Sumatra, and the global incidence rate is 6%[4].

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Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 79/E/KPT/2023; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v11-I.1.2025.47-53

Anaplastic lymphoma kinase (ALK) is one of the oncogenes that is being researched extensively. The ALK gene is located on chromosome 2 area 2p23.2-p23.1. As an oncogene, ALK is expressed in several specific areas. When ALK fusion occurs, the formation of dimers from the ALK fusion will cause activation of the ALK protein kinase area which plays an important role in the tumorigenic process. Partner proteins will control fusion behavior, such as expression and activation levels so that these cells will proliferate, survive, differentiate, and migrate which will ultimately lead to cancer[5].

ALK examination is carried out at the molecular level, to detect the presence of fusion protein expression. ALK rearrangements can be detected using a variety of methods. The most frequently used methods are ALK fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), ALK immunohistochemistry (IHC), RNA sequencing by next-generation sequencing (RNA-seq NGS), and DNA sequencing by next-generation sequencing (DNA-seq NGS). Patients who are ALK-positive are candidates for therapy with ALK inhibitors[6].

The presence of the ALK fusion protein, as well as the ALK tyrosine kinase activity, is a therapeutic target in all ALK-rearranged cancers. In addition, because ALK is not widely expressed in adult human tissue, few toxic effects would occur if ALK function were inhibited. The first ALK inhibitor introduced in the therapy of ALK-dependent NSCLC was crizotinib, a potent ALK tyrosine kinase inhibitor molecule. Crizotinib's toxicity, resistance, and limitations led to the study of second and third-generation ALK inhibitors[5].

Clinical trials for several second and third-generation ALK inhibitors are ongoing or completed. Secondary resistance mutations discovered in patients receiving crizotinib therapy can be inhibited by second-generation inhibitors, including ceritinib, alectinib, and brigatinib. The majority of these inhibitors exhibit activity that prevents resistance to crizotinib. Compared to crizotinib, second-generation ALK inhibitors are more effective in the central nervous system and have a higher affinity for the ALK fusion gene. For patients who cannot tolerate crizotinib or who continue developing disease progression, the Food and Drug Administration (FDA) has approved these second-generation inhibitor agents[7].

The only third-generation ALK inhibitor currently available is lorlatinib (PF-06463922). Lorlatinib is a potent and reversible small molecule that inhibits ROS1 and ALK. These third-generation inhibitors are effective against all resistance types discovered to date. Lorlatinib was created to enhance brain penetration and overcome the problem of resistance to first and second-generation ALK inhibitors[8].

METHODS

Study Design and Eligibility Criteria

This study used non-probability consecutive sampling to enroll 34 patients with lung adenocarcinoma. The study was conducted at several hospitals in Medan, including H. Adam Malik Hospital, USU Hospital, and Santa Elisabeth Hospital, to collect research subjects with lung cancer that was histopathologically diagnosed with adenocarcinoma. Clinical data will be collected from medical records, including age, gender, staging (pTNM stage), organ metastases, smoking habits, and ethnicity. Patients' formalin-fixed paraffin-embedded (FFPE) will borrowed from each hospital for ALK rearrangement detection. The inclusion criteria were: 1) pathologically confirmed diagnosis of adenocarcinoma (NSCLC); 2) male and female lung cancer patients; 3) age ≥18 years. The exclusion criteria were as follows: 1) Incomplete medical record data, and 2) Patient FFPE or histopathological tissue that is neither acceptable nor insufficient.

ALK Rearrangement Detection

The procedure for ALK immunohistochemistry (IHC) utilizing a corresponding negative control and the highly sensitive anti-ALK (D5F3) rabbit monoclonal primary antibody (Ventana Medical Systems Inc., Tucson, AZ, USA) is carried out by a specific protocol designed to detect ALK protein expression in formalin-fixed paraffin-embedded tissue sections. Patients' formalin-fixed paraffin-embedded (FFPE) tissue is sectioned into thin slices (typically 3-5 µm) and mounted onto positively charged glass slides. The tissue slides are deparaffinized in xylene or a xylene substitute to remove the paraffin wax and stained with H&E, pathologist will ensure that there are enough tumor cells to be examined. Ventana anti-ALK (D5F3) Rabbit Monoclonal Primary Antibody is applied to the tissue sections, this antibody specifically binds to the ALK protein in the sample, if it is present. All steps are typically done using a Ventana automated system.

Ventana OptiView DAB (diaminobenzidine) chromogen is used as the detection reagent, which produces a brown precipitate at the site of the ALK protein-antibody complex, making the signal visible under a microscope. The slides are counterstained with hematoxylin, which stains the nuclei of the cells, providing contrast to the DAB staining. A pathologist examines stained tissue sections under a light microscope. Positive staining for ALK is indicated by

brown cytoplasmic staining in tumor cells, while negative staining shows no brown signal. A pathologist will assess the intensity and percentage of tumor cells showing ALK expression to determine ALK status. The D5F3 clone often gives a strong binary positive/negative result, making interpretation more straightforward and according to the Ventana anti-ALK (D5F3) IHC assay Clinical Scoring Algorithm for NSCLC.

Data Analysis

Clinical and demographic information was collected and displayed as percentages and frequencies. Each variable was displayed using univariate analysis. The Statistical Program for Social Sciences (SPSS) version 24.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

RESULTS

34 of the 52 participants in this study met the requirements for inclusion and were able to identify their ALK status. Other participants were removed from this study due to missing medical record data or insufficient FFPE for the ALK IHC examination (Figure 1).

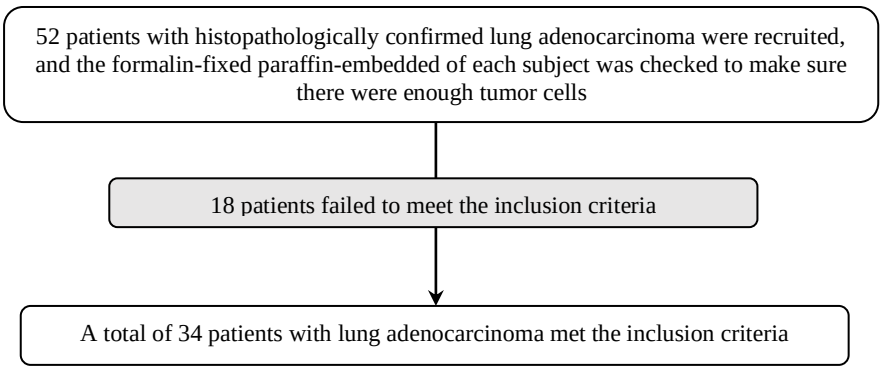

Figure 1. Flow chart of ALK rearrangement in lung adenocarcinoma

According to the study findings, the majority of research subjects were over 60 (52.9%), followed by those between 41 and 60 (44.2%), and there was only one research sample with participants between the ages of 18 and 40 (2.9%). In this study, 61 was the average age. Gender-wise, the research sample's lung adenocarcinoma patients were predominantly male (76.4%) and female (23.6%). Based on race and ethnicity, the samples were distributed, with Minang having 9 samples (26.4%) and Batak/Karo having 19 samples (55.8%)—the largest group. Only five samples (14.7%) had never smoked, according to the degree of smoking, while 24 samples (70.6%) were heavy smokers. Based on pTNM stage, the research sample's characteristics showed that the majority of lung adenocarcinoma patients (70.6%) were at Stage IVA, followed by Stage IIIB (8 cases; 23.6%), with no cases at Stage IIIA or lower. From this study, it was found that 32 cases (94.2%) had negative expression of ALK fusion protein in lung adenocarcinoma, while 2 cases (5.8%) had positive expression. Both ALK-positive subjects were stage IVA and had pleural metastases (100%).

Table 1. Prevalence of anaplastic lymphoma kinase (ALK) rearrangement

ALK Rearrangement	Total	
	N	%
ALK rearrangement positive (+)	2	5.8
ALK rearrangement negative (-)	32	94.2

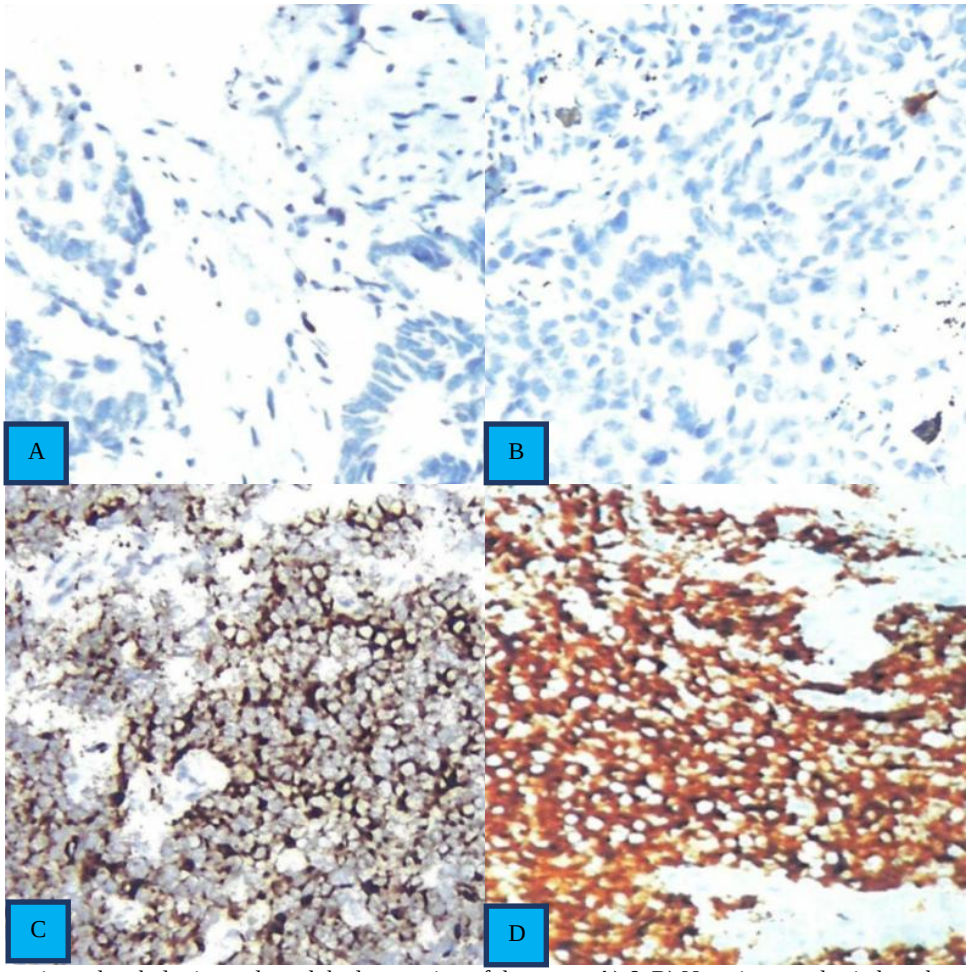

Figure 2. An experienced pathologist evaluated the last portion of the exam. A) & B) Negative anaplastic lymphoma kinase (ALK) immunohistochemistry (IHC) examination results; C) & D) Positive ALK IHC examination results showed strong and diffuse staining.

Table 2. Characteristics of anaplastic lymphoma kinase (ALK) rearrangement mutation samples

Characteristics	ALK Rearrangement		Total (%)
	Positive (%)	Negative (%)	
Age			
<40 years old	0 (0)	1 (3.1)	1 (2.9)
41-60 years old	1 (50)	14 (43.8)	15 (44.1)
>60 years old	1 (50)	17 (53.1)	18 (52.9)
Sex			
Male	1 (50)	24 (75)	25 (73.5)
Female	1 (50)	8 (25)	9 (26.5)
Smoking status			
Never smoker	0 (0)	5 (15.6)	5 (14.7)
Mild smoker	0 (0)	4 (12.5)	4 (11.8)
Moderate smoker	0 (0)	1 (3.1)	1 (2.9)
Heavy smoker	2 (100)	22 (68.8)	24 (70.6)
pTNM stage			
IIIB	0 (0)	8 (25)	8 (23.5)
IIIC	0 (0)	1 (3.1)	1 (2.9)
IVA	2 (100)	22 (68.8)	24 (70.6)
IVB	0 (0)	1 (3.1)	1 (2.9)
Organ metastases			
No metastases	0	9 (28.1)	9 (26.5)
Pleura	2 (100)	20 (62.5)	22 (64.7)
Hepar	0	2 (5.9)	2 (5.9)
Brain	0	2 (5.9)	2 (5.9)
Others (bone, axilla, colli, pericardium, vertebra, plica vocalis)	0	6 (17.6)	6 (17.6)
Total	2 (100)	32 (100)	34 (100)

DISCUSSION

ALK rearrangement is one of the many traits and molecular involvements of lung cancer. In this study, cases of lung adenocarcinoma that had ALK mutations were found in 2 cases (5.8%) and ALK was found to be negative in 32 cases (94.2%). A study by Koivunen et al. has the same trend as the NSCLC sample, the ALK fusion gene was identified in 1% of Americans and 3% of Korean patients[9]. A previous study in Hong Kong showed that the frequency of ALK in NSCLC was 4.9%, none of the patients had ever been examined for EGFR mutations. In that study, EGFR positivity was later discovered in 46.9% of samples[10]. This suggests that among NSCLC patients who were not previously screened, EML4-ALK rearrangements are quite uncommon (1–5%). According to a study, up to 22% of screened adenocarcinoma patients with a history of non-smokers or light smokers had ALK mutations[11]. Ren et al's study showed that the prevalence of lung adenocarcinoma with wild-type EGFR mutation and EML4-ALK rearrangement could reach 32% in nonsmokers[12]. In line with a study in Indonesia by Heriyanto et al., which demonstrated that in lung adenocarcinoma cytology specimens with negative EGFR mutations, the prevalence of ALK was 20%[13].

Oktaviyanti's study showed that the sample of adenocarcinoma sufferers aged 18 - 40 years was 7 cases (18.4%), 41 - 60 years was 17 cases (44.7%), and >60 years was 14 cases (36.8%)[14]. Slightly different from the study's findings, which showed that the majority of the sample—18 cases, or 52.9%—were in the age range of 60 years or older. According to study by Fauziah (2019), from 2012 to 2017, most patients diagnosed with lung adenocarcinoma at the Department of Anatomical Pathology, Dr. Hasan Sadikin General Hospital, were aged >40 years. This percentage reached up to 90%[15]. The study is consistent with the current investigation, which found that there was only 1 instance (2.9%) involving a patient who was younger than 40 years.

A Purnawati et al. meta-analysis on the characteristics of lung adenocarcinoma patients in Indonesia found that the age of lung cancer patients varied. Of the 19 journals that gathered data on the average age of lung cancer patients, 17 journals reported that the majority of these patients were older than 40, and 2 other journals reported that the majority of these patients were younger than 40. Most lung cancer cases start in adulthood, according to the pathogenesis theory of the disease's course, supported by the 17 journals. This is brought on by early-life prolonged exposure to carcinogenic substances and aging-related immune system deterioration, which promote carcinogenesis[16].

The research subject's characteristics indicated their degree of smoking, with 24 samples (70.6%) being heavy smokers. The primary cause of all forms of lung cancer is smoking. It is widely acknowledged that smoking causes lung cancer and that the length of a smoker's smoking history is the most significant predictor of their risk of developing lung cancer. Lung cancer is not caused by nicotine, although it can lead to cigarette addiction. The primary carcinogen found in cigarettes is continuous exposure to tar[17]. However, according to Fauziah's (2019) study, 75% of the lung cancer patients diagnosed between 2012 and 2017 were non-smokers, whereas the remaining patients smoked[15]. The high incidence of lung adenocarcinoma in non-smoking patients is related to the subtype of lung adenocarcinoma itself[17].

Arumsari et al. (2019), Aktalina et al. (2019), and Soeroso et al. (2021) gathered information on lung cancer patients with a higher Brinkman Index severity. From these three journals, it may be concluded that smoking increases the risk of lung cancer[4,18,19]. According to data on the distribution of cancer stages, most study participants were in stage IV. Sanchez Lara's research yielded similar results, supporting the theory that the prevalence of advanced-stage lung cancer is higher than that of the early stage because the latter is typically characterized by non-specific symptoms or no symptoms at all, making an early diagnosis difficult[20,21].

In our research, we are using FFPE tissue sample form biopsy whether it is transthoracic biopsy or transbronchial biopsy. For the diagnosis of non-small cell lung cancer (NSCLC) and the identification of histological subtypes, tissue biopsy is the gold standard. It is also used for some predictive biomarker assessment using molecular biology testing (one gene sequencing and NGS methods), IHC (like immunostaining for PD-L1 and ALK), and FISH (ALK, ROS1, and MET). Furthermore, a tissue biopsy typically has a higher sensitivity for fusion and copy number variation detection than a liquid biopsy, especially when the tumor fraction in cf-DNA is small (<1%)[22].

Immunohistochemistry or IHC examination in pathology practice has been widely used because it is fast, economical, and simple. IHC has been recommended as an alternative detection method for ALK rearrangement. IHC testing is a suitable and reliable alternative to FISH for the detection of ALK-positive NSCLC[23]. The Ventana ALK (D5F3) CDx assay was specifically developed to maximize agreement with ALK FISH testing and to enable the use of ALK IHC as a standalone companion diagnostic test to identify patients with ALK-positive NSCLC eligible for treatment with crizotinib[24].

ALK rearrangement is affiliated with advanced stages at the process manifestations appear. In addition, patients with ALK-positive were observed to have a special pattern of disease spread. In one report of advanced-stage patients, ALK rearrangement was significantly associated with pericardial, pleural, and hepatic metastases compared with ALK-negative patients[25]. The patients in this study who tested positive for ALK had metastases to the pleura and were in stage IVA.

CONCLUSION

Lung adenocarcinoma patients in this study were mostly male, older than 60 years old, and heavy smokers. According to immunohistochemical analysis, 5.8% of lung adenocarcinoma cancer patients had an ALK rearrangement mutation. There are relatively few ALK rearrangement mutations in lung adenocarcinoma patients without screening. Additional research is required to ascertain the characteristics distribution of lung adenocarcinoma patients that are associated with a higher prevalence of ALK rearrangement mutations.

Acknowledgments
None declared.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
None declared.

Authors' Contributions
Concept or idea, design, and research substance: MYAP, NNS, DA and DWTL. Collected data by searching the literature and obtained information: MYAP and NNS. Data analysis and research methodology: MYAP, NNS and TA. Manuscript preparation, editing, and review: MYAP, NNS, DA, TA, and DWTL. All authors contributed and approved the final version of the manuscript.

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