

ORIGINAL ARTICLE

Prevalence of Lung Cancer with a History of Tuberculosis

Nadira Putri Nastiti¹, Laksmi Wulandari^{2*}, Sulistiawati Sulistiawati³, Anna Febriani²,
Wiwin Is Effendi⁴

¹Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

²Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia.

³Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

⁴Department of Internal Medicine, Division of Respiratory Medicine, Graduate School of Medicine, Kobe University, Kobe, Japan.

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ABSTRACT

Introduction: Lung cancer ranks as the second most common diagnosis of malignancy cases in the world with the highest mortality, while Indonesia is the country with the largest tuberculosis (TB) burden after India. Although these two diseases have a high incidence and mortality rate and are one of the main causes of health problems, coexistence between these two diseases is very rare. A similar clinical and radiological feature complicates the diagnosis and worsens the prognosis. This study aimed to determine the prevalence and distribution patterns of lung cancer incidence with a history of TB.

Methods: This was a descriptive study. The data were obtained retrospectively from the electronic medical records of lung cancer patients from one roof oncology clinic, Dr. Soetomo General Hospital, Surabaya, in 2018–2020, meeting the inclusion and exclusion criteria.

Results: Specifically, 76 out of 1,044 (7.3%) lung cancer patients had a history of TB, with the distribution being men (71.1%), in an age range of 50-59 years old (34.2%), who were active smokers (36.9%), had an adenocarcinoma type of cancer (90.8%), had a positive EGFR gene mutation (50%), and had a diagnosis of non-small cell lung cancer (NSCLC) during stage IV (79%) after a TB diagnosis (54%) with a time interval of 1 or >10 years.

Conclusion: The prevalence of lung cancer with a history of TB was 7.3%. Lung cancer screening is important in TB patients after one or even >10 years of diagnosis to reduce the morbidity and mortality rates because of this risk of coexistence.

INTRODUCTION

Lung cancer occurs due to uncontrolled cell proliferation in the lungs that tends to damage normal tissue with the possibility of metastasizing to other organs.^{1,2} This disease is the second most common diagnosis of malignancy cases worldwide, with the highest mortality.³ Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (MTB), with the lungs as the main localization organ. Globally in 2020, TB became the infectious disease with the second-highest mortality after COVID-19. Indonesia is still the country with the largest TB burden in the world after India.⁴ Although lung cancer and TB are two diseases with a high incidence and mortality, the coexistence between these two diseases is very rare. Based on previous

studies, case studies regarding lung cancer with TB have been widely reported. Dacosta and Kinare (1991) obtained a prevalence result of 13.1% for patients who had a combination of lung cancer and TB.⁵ Watanabe, et al. (2007) reported the coexistence of lung cancer with TB was 2.1%.⁶

The relationship between the incidence of lung cancer with TB is not yet known with certainty. Still, there have been hypotheses that explain the possible mechanisms by which these two diseases occur. The plausible mechanisms include where TB increases the risk of lung cancer, lung cancer causes the reactivation of MTB, or the two diseases appear together without a relationship.⁷ One study outlined the various hypotheses regarding the coexistence of the two diseases.² The first one was that a carcinoma occurs in the TB area and

*Corresponding author: laksmi.wulandari@fk.unair.ac.id



causes the reactivation of the old foci lesions of TB. Next was where a carcinoma developed from TB scarring. Lung cancer and TB are independent but can occur in a comparable period. The last is the secondary infection of cancer with TB.

Delays in lung cancer diagnosis in patients with a history of TB occur because of the similarity in clinical manifestations and pictures of lesions upon a radiological examination. This causes a new diagnosis to be established when the cancer stage has become advanced.^{8,9} Although there have been several case reports regarding the incidence of coexistence between lung cancer and TB, studies in Indonesia are still lacking. This study aimed to determine the prevalence and distribution pattern of lung cancer alongside a history of TB to help health workers reduce the morbidity and mortality rate.

METHODS

This was a descriptive study performed in one roof oncology clinic in the division of lung cancer, Dr. Soetomo General Hospital, Surabaya. The population of this study was all lung cancer patients from one roof oncology clinic, Dr. Soetomo General Hospital, Surabaya, from 1 January 2018 to 31 December 2020. The sample used was all patients who met the inclusion criteria, specifically patients with a history of TB, known by their history of anti-TB drugs (ATD) consumption. The exclusion criteria were patients with an incomplete medical record and a diagnosis not of primary lung cancer.

This study used the total sampling technique by collecting all of the patient's medical records who met the inclusion and exclusion criteria. The subjects were assessed based on the incidence of TB, gender, age, history of smoking, type of lung cancer based on the histopathology, epidermal growth factor receptor (EGFR) gene mutation, the time of the lung cancer diagnosis compared to TB diagnosis, and the stage of lung cancer when first diagnosed. The time of lung cancer diagnosis was determined by comparing it with the history of TB. Whether the lung cancer was established simultaneously with the TB findings, after having had a TB diagnosis in the past, or where lung cancer was established before TB means the patient had lung cancer first and then the TB disease. This was a retrospective study using the electronic medical records of lung cancer patients at Dr. Soetomo General Hospital, Surabaya, who met the inclusion criteria as the instrument. The data were pooled, processed, and analyzed descriptively. This study received ethical clearance from the Ethical Committee Dr. Soetomo

General Hospital, Surabaya, with a signed ethical approval number 0920/127/4/IX/2021.

RESULTS

Of all 1,044 patients who suffered from lung cancer at Dr. Soetomo General Hospital, Surabaya, from 1 January 2018 to 31 December 2020, 76 (7.3%) patients determined TB coexistence according to ATD consumption history. The study subjects comprised 54 (71.1%) males and 22 (28.9%) females. The youngest patient was 29 years old, and the oldest was 87, with a mean and median age of 59.5 years old. In dominance, the samples were in the age range of 50–59 years old.

Table 1. Prevalence of lung cancer with a history of TB

History of TB	n	Percentage (%)
Lung cancer with a history of TB	76	7.3%
Lung cancer without a history of TB	968	92.7%
Total	1,044	100

Table 2. Sample characteristics

Variable	76 (%)
Gender	
Female	22 (28.9%)
Male	54 (71.1%)
Age (years old)	
<50	12 (15.8%)
50-59	26 (34.2%)
60-69	25 (32.9%)
≥70	13 (17.1%)
History of smoking	
Smoker	28 (36.9%)
Non-smoker	14 (18.4%)
No data	34 (44.7%)
Type of lung cancer	
Adenocarcinoma	69 (90.8%)
Squamous cell carcinoma	7 (9.2%)
Large cell carcinoma	0 (0%)
Small cell carcinoma	0 (0%)
Other types	0 (0%)
EGFR gene mutation	
Positive	38 (50%)
Negative	28 (36.8%)
No data	10 (13.2%)
Time of lung cancer diagnosis compared with TB diagnosis	
Coincided with TB diagnosis	28 (36.8%)
After TB diagnosis	41 (54%)
Before TB diagnosis	0 (0%)
No data	7 (9.2%)
Stage of lung cancer diagnosis	
NSCLC stage I	0 (0%)
NSCLC stage II	0 (0%)
NSCLC stage III	10 (13.2%)
NSCLC stage IV	59 (77.6%)
SCLC limited stage	0 (0%)
SCLC extensive stage	7 (9.2%)

EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer

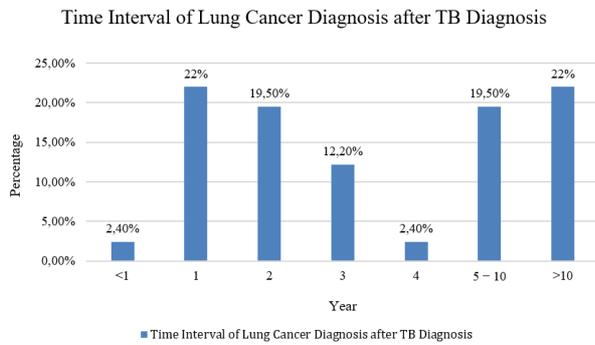


Figure 1. The time interval of lung cancer diagnosis after TB diagnosis

For smoking history, the number of smoking patients was found to be more than non-smokers, with a percentage of 36.9% and 18.4%, respectively. However, 44.7% of subjects had no data on their smoking history. The collected data from smoking patients also resulted in 14 cigarettes per day as the mean cigarette consumption, with a range of 2–32 cigarette sticks per day. The type of lung cancer distribution based on histopathology in 76 patients found that most had the adenocarcinoma type, followed by squamous cell carcinoma totaling 69 (90.8%) and 7 (9.2%) samples, respectively. There were no other types of lung cancer discovered in this observational study. Half of the subjects were also positive for EGFR gene mutation, whereas 10 (13.2%) subjects had no data.

The time of lung cancer diagnosis compared to TB diagnosis was observed in this study, and it was dominated by lung cancer diagnosis after TB, where both diseases occurred simultaneously. The subjects were 41 (54%) and 28 (36.8%). Lung cancer diagnosed before TB was not found in this study. Additionally, among 41 cases of lung cancer diagnosed after TB, most patients were diagnosed with lung cancer after one or >10 years in terms of the time interval. The time interval range was eight months to 40 years, with 6.74 years as the mean and three years as the median. This study found that most subjects were diagnosed with NSCLC stage IV (77.6%) and stage III (13.2%). There were no cases found for stages I or II. For SCLC, all patients were diagnosed at an extensive stage.

DISCUSSION

Coexistence between lung cancer and TB is a rare occurrence but can correlate with each other. The results of the study conducted by Aoki, *et al.* (2016) in Japan from 2007 to 2015 stated that the incidence of lung cancer with TB was 1.38%.¹⁰ This is not much different from the study conducted in Lithuania for 15 years, which reported that as many as 46 patients out of 2,218

with lung cancer (2.1%) had a history of TB.⁶ The incidence of TB in lung cancer patients was also studied in India in 1991 by Dacosta, *et al.* (1991) and resulted in a prevalence rate of 13.1%.⁵ In one of the reports by Nuessle, it was stated that the prevalence of the coexistence of lung cancer with TB in the United States was 6.3%.¹¹

The prevalence of TB in lung cancer patients in this study resulted in a higher rate of 7.3% compared to other studies in lower-burden TB countries such as Japan, Taiwan, European countries, and the United States.¹¹ This is due to Indonesia being an area with endemic TB. The high level of cigarette consumption, exposure to pollutants, and the large population of households with low socioeconomic increase the prevalence of TB among lung cancer patients in Indonesia.¹² In contrast, the incidence rate from this study compared to the incidence in India was lower. This may also happen concerning India, the country with the largest TB burden in the world, followed by Indonesia.⁴ This study shows that the coexistence of the two diseases can vary according to the place and time the study was conducted.

Gender

This study found that the majority of patients with the coexistence of lung cancer and TB were males at a percentage of 71.1%. The result for gender distribution in this study is in line with a previous study conducted by Silva in Brazil, which examined 24 patients with lung cancer with TB.¹³ Specifically, 14 were males, and 10 were females, representing 58.3% and 41.7%, respectively. Another study conducted in Japan also found a dominance of males over females with distributions of 93.75% and 6.25%.¹⁴ Males tend to have a higher risk of cigarette smoke and pollutants exposure based on their occupation, longer outdoor activity, and smoking habit.¹⁵

Age

The mean age of the subjects in this study was 59.5 years old, with most being 50–59 years old. This result is consistent with another study by An in Korea which stated that the risk of lung cancer in younger TB patients was higher than in the elderly.¹⁵ Hence, TB patients at a younger age should have a further evaluation to rule out the coexistence of lung cancer.¹⁶ The cohort TB study conducted in Taiwan also showed that the lung cancer incidence rate ratio was higher in patients aged under 60 years old than over 60.¹⁷ The explanation regarding how age affects the course of lung cancer coexistence with TB is still uncertain and needs data, as well as clinical studies.

History of Smoking

Based on this study, the number of smokers was more than the number of non-smokers at a percentage of 36.9%, although there were still 44.7% of patients with no data on their smoking history. Lung cancer and TB remained related even after their cigarette consumption was controlled. Their cancer risk was 2.5 times higher in TB patients.¹³ A result from the previous studies conducted in Korea showed that smoker TB patients had a higher risk of lung cancer than ex-smokers, while it was less in non-smokers.¹⁸ However, the study stated that because there was not much difference in the risk rates between smokers and non-smokers, TB could be a risk factor for the progressiveness of lung cancer without a smoking history.

Type of Lung Cancer

NSCLC adenocarcinoma dominated the type of lung cancer in this study. Of all subjects, 90.2% had adenocarcinoma, and only 9.2% had squamous cell carcinoma. No other types of lung cancer were found among the patients. These results were in line with a previous study from Japan which showed that 55.6% of lung cancers with TB were of the adenocarcinoma type.¹⁰ Another study also reported that the percentage of adenocarcinoma in lung cancer coexistence with TB was 58.3%, followed by epidermoid carcinoma at 25%.¹³ In patients suffering from both lung cancer and TB, adenocarcinoma type has the highest frequency, whereas squamous and small cell carcinoma both had no significant relation with TB.¹⁹

However, this observational study had different results in comparison to a study conducted by Cicenac which found that 52.2% of patients with lung cancer coexistent TB had epidermoid carcinoma and only 21.7% had the adenocarcinoma type.⁶ Other studies also discovered that the foremost lung cancer types were planocellular carcinoma, squamous cell, and adenocarcinoma.²

EGFR Gene Mutation

In this study, half of the samples indicated a positive mutation in EGFR. A study conducted in Taiwan also found an increased incidence of EGFR gene mutation that was higher in patients with an adenocarcinoma type of lung cancer with a history of TB lesions compared to those with no TB lesions.¹⁹ There was a significant relationship between lung cancer patients who had old TB lesions and an increased probability of EGFR gene mutation, particularly deletion in exon 19.¹¹ Other studies also showed that the percentages of EGFR mutation were higher in patients with a history of TB than those who did not have the mutation.^{20,21}

EGFR mutations in lung cancer patients and their relationship with a history of TB lesions caused by TB in the form of local and chronic inflammation support the lung carcinogenesis process by triggering genetic changes.²¹ Matsuda, *et al.* (2019) provided an overview of the course of this process where oxidants triggered the metaplasia of goblet cells in the bronchial epithelium, triggering the activation of EGFR.²¹ This invasive mutation of EGFR is affected by overexpression in the epiregulin triggered by the presence of TB infection.²¹

Timing of the Lung Cancer Diagnosis Coexistence with TB

This study showed that 54% of patients had lung cancer diagnosed after TB, while the rest occurred simultaneously. Lung cancer was diagnosed mostly after one year or >10 years. The median of the interval years was 5 years with an interquartile range of 1–9 years. These results align with a previous study that reported that 58.3% of subjects also had a TB diagnosis first before lung cancer, 41.7% coincidentally, and where there was no TB diagnosis after lung cancer.¹³ A study conducted in Bosnia also stated that the lung cancer patient's coexistence with TB dominated with them having a lung cancer diagnosis first, then TB, with the median of interval years being 5 years and with 2–25 years being the interquartile range.²

The risk of lung cancer is higher in the first 5 years after TB is diagnosed. However, the risk is still 1.99 times higher even when the interval years of both diseases has reached 20 years.² Another study stated that the risk of lung cancer was the highest in the first 2 years after TB had been diagnosed.⁷ Similarly, a study from Korea stated that the risk of lung cancer is the highest in the first year after TB is diagnosed.¹⁵

From this observation, the incident of lung cancer simultaneously with TB occurred in 36.8% of subjects. In this case, the chronology of the course of lung cancer and TB means that it cannot be clearly known whether lung cancer is preceded by TB infection or vice versa. Difficulty in diagnosing the coexistence of these two diseases causes frequent misdiagnoses, missed diagnoses, or delays in diagnosis.²²

Stage of Diagnosis

In this study, almost all patients suffering from lung cancer with a TB history were diagnosed with lung cancer in stage IV, while 13.2% were diagnosed in stage III. There were no patients diagnosed at stage I or II. The result of most patients being diagnosed at stage IV was in line with a previous study conducted in Japan, in which 50% of subjects were diagnosed with lung cancer at stage IV, then 31.2% at stage II, and 18.8% at stage

III.¹⁴ In Lithuania, a study reported that 50% of patients were diagnosed at stage III and only a few at stages I and II.⁶

Simultaneously occurring lung cancer and T in the same organ also makes it difficult to determine whether lung cancer is caused by TB, which was suffered first, or vice versa. Often an established diagnosis for one of the diseases tends to disguise the other disease, making the diagnosis of lung cancer in patients with a history of TB very rare in the early stages of cancer.¹⁵ Early diagnosis is important in patients with lung cancer and TB coexistence due to the need to begin appropriate and immediate treatment.²³ Parker, *et al.* (2018) recommended that patients with high-risk factors for lung cancer, namely >55 years old with a history of smoking >30 packs per year, should be evaluated using a CT scan aimed to determine the presence of malignancies in the lungs even where there has been a clinical and microbiological diagnosis of TB.²⁴

CONCLUSION

This study shows that the prevalence of lung cancer with a history of TB was 7.3%. The subjects were dominated by males aged 50–59 years old, who were smokers, had an adenocarcinoma type of lung cancer based on the histopathology, and had a positive EGFR gene mutation. Lung cancer diagnosis was mostly established after one or >10 years of TB diagnosis in stage IV. Patients with TB or lung cancer require a further and thorough evaluation of their examinations to rule out this coexistence because early diagnosis is important to start appropriate and effective therapy. Furthermore, according to the findings of this study, lung cancer screening is important in TB patients after one and >10 years of diagnosis to reduce the morbidity and mortality rates.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Concepting, designing, collecting data, and interpreting results: NPN and LW. Manuscript writing and revising: NPN, LW, SS, AF, WIE. All authors contributed and approved the final version of the manuscript.

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