Vol. 5, No. 2, February 2025

e-ISSN 2474-1306

Official Journal of The Indonesian Society of Respirology

RESPIRATORY Science

- Correlation Between Coinfection of Severe and Critically Ill COVID-19 Patients In Intensive Care Unit with Leucocyte, Neutrophil, CRP, Procalcitonin and Length of Stay
- Effect of Body Mass Index, Sputum Conversion Status, and Adverse Drug Events Severity On Health-Related Quality of Life of Drug-Resistant Tuberculosis Patients
- Respiratory Rehabilitation for A Loss to Follow-Up Pulmonary Tuberculosis Patient with Bilateral Hydropneumothorax: A Case Report
- Cutaneous Adverse Drug Reaction due to Anti-TB Drug Allergy in TB-HIV Patient: A Case Report
- The Impact of Klotho Gene Polymorphisms on Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review
- Diagnosis and Management of Interstitial Lung Abnormalities (ILA): An Article Review
- Exploring Epigenetic Landscapes in COPD: Therapeutic Implications and Recent Insights
- The Evolution of Transbronchial Lung Biopsy Guidance

Website: http://www.jurnalrespilogi.org

RESPIRATORY Science

Official Journal of The Indonesian Society of Respirology

Editorial Office
The Indonesian Society of Respirology
Jl. Cipinang Bunder, No. 19, Cipinang, Pulo Gadung
Jakarta Timur, Indonesia, 13240 Telp: 02122474845
Email: respirologyscience@gmail.com
Website: https://respiratoryscience.or.id/

Publisher
The Indonesian Society of Respirology

RESPIRATORY Science

Official Journal of The Indonesian Society of Respirology

VOLUME 5, NUMBER 2, February 2025

Table of Content

Correlation Between Coinfection of Severe and Critically Ill COVID-19 Patients In Intensive Care Unit with Leucocyte, Neutrophil, CRP, Procalcitonin and Length of Stay 62
Harman Prayitno, Yani Jane Sugiri, Tri Wahju Astuti, Arie Zainul Fatoni, Nurima Diyah Puji Hastuti

Effect of Body Mass Index, Sputum Conversion Status, and Adverse Drug Events Severity On Health-Related Quality of Life of Drug-Resistant Tuberculosis Patients 72
Sandy Kurniawan, Jatu Aphridasari, A Farih Raharjo

Respiratory Rehabilitation for A Loss to Follow-Up Pulmonary Tuberculosis Patient with Bilateral Hydropneumothorax: A Case Report 82
Rezky Ahmad Isdiyanta[1], Siti Chandra Widjanantie

Cutaneous Adverse Drug Reaction due to Anti-TB Drug Allergy in TB-HIV Patient: A Case Report 92
Dewi Behtri Yanifitri, Yunita Arliny, Rahmi Hayati

The Impact of Klotho Gene Polymorphisms on Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review 99
Derallah A Lindra, Endang Purwaningsih, Ahmad Rusdan H Utomo, Faisal Yunus, Makrup E Harahap

Diagnosis and Management of Interstitial Lung Abnormalities (ILA): An Article Review 115
I Wayan Pande Adhyaksa, Fanny Fachrucha

Exploring Epigenetic Landscapes in COPD: Therapeutic Implications and Recent Insights 126
Aditya Wirawan, Tutug Kinasih, Rania Imaniar, Hario Baskoro, Budhi Antariksa, Naohisa Matsumoto

The Evolution of Transbronchial Lung Biopsy Guidance 141
Mohamad Fahmi Alatas, Asri Liqditta Bies, Prasenohadi, Dicky Soehardiman, Wahju Aniwdyaningsih, Mia Elhidsi, Ginanjar Arum Desianti, Tina Reisa, Menaldi Rasmin

Original Article

Correlation Between Coinfection of Severe and Critically Ill COVID-19 Patients In Intensive Care Unit with Leucocyte, Neutrophil, CRP, Procalcitonin and Length of Stay

Harman Prayitno[1], Yani Jane Sugiri[1], Tri Wahju Astuti[1], Arie Zainul Fatoni[2], Nurima Diyah Puji Hastuti[3]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang
[2]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang
[3]Department of Clinical Microbiology, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang

Corresponding Author:
Harman Prayitno | Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, Brawijaya University, Dr. Saiful Anwar General Hospital, Malang | Dr.harman.prayitno@gmail.com

Submitted: January 15th, 2024
Accepted: January 25th, 2025
Published: February 28th, 2025

Respir Sci. 2025; 5(2): 62-71
https://doi.org/10.36497/respirsci.v5i2.167

Abstract

Background: Severe or critical COVID-19 infections are linked to admissions in the intensive care unit (ICU), which increases the risk of coinfection and results in a worsened prognosis. This research seeks to evaluate the relationship between bacterial and fungal coinfection in COVID-19 and leukocyte, neutrophil, C-Reactive Protein (CRP), procalcitonin levels, length of stay, and outcome (whether the patient was discharged from ICU to the ward or died).

Method: This research constitutes a retrospective cohort analysis. Data was collected from the medical records of patients admitted to the ICU of Saiful Anwar General Hospital in Malang from August 2020 to August 2021, who tested positive for COVID-19. A total of 352 individuals qualified according to the inclusion criteria.

Results: Coinfection occurred in 22.2% of COVID-19 patients, with bacterial 84.61%, fungal 11.53%, and both bacterial and fungal 3.84%. The average stay for patients without coinfection was 6 days, while it was 13 days for those with coinfection. We also observed a rise in mortality rate for coinfection at 71.8% compared to 31% for non-coinfection. Coinfection with bacterial, fungal, or both types in COVID-19 shows a positive correlation with Leucocyte (P=0.001; r=0.356), Neutrophil (P=0.001; r=0.438), CRP (P=0.003; r=0.164) and Procalcitonin (P=0.001; r=0.192) as well as a positive correlation with the length of stay (P=0.001) and a negative correlation with the outcome (P=0.001).

Conclusion: Coinfection occurred in just about one-fifth of COVID-19 patients. We suggest prescribing antimicrobials only when there is a compelling reason. Timely detection of bacterial and fungal coinfection was essential to identify high-risk patients and determine appropriate interventions to prevent longer hospital stays and reduce mortality.

Keywords: COVID-19, coinfection, length of stay, mortality

INTRODUCTION

In Wuhan, China, around the end of 2019, there was a pneumonia case without a known cause. In certain cases, severe symptoms of respiratory tract infection occur, including acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), and other serious complications. Later, a new coronavirus was identified by the Chinese Centre for Disease Control and Prevention (CDC) and named 2019 – nCoV by WHO.[1]

The WHO declared the novel coronavirus (COVID-19) outbreak a pandemic on March 11, 2020. In its report, the WHO expressed concern about the spread and severity of the disease. According to the most recent COVID-19 pandemic reports, there have been 3,167,039 deaths and 150,359,096 confirmed cases of the virus worldwide, which is a significant number in many nations, including Indonesia.[2]

Co-infection with SARS-CoV-2 has received less research attention, as most studies focus only on SARS-CoV-2. Coinfections with certain pathogens can also hinder an accurate diagnosis of the disease. In addition to providing information on bacterial and fungal infections, Wang et al offer the most recent SARS-CoV-2 coinfection status in China.[3] The type and prevalence of co-infections in SARS-CoV-2-positive patients remain uncertain.

Bacterial and fungal infections are common complications of viral pneumonia, especially in critically ill patients. Bacterial and fungal coinfections increase the need for intensive care and increase mortality. In influenza patients, bacterial co-infection occurs in ~0.5% of healthy young individuals and at least 2.5% of older individuals.[4]

Several factors increase the risk of developing bacterial and fungal infections in COVID-19 patients. First, the action of SARS-CoV-2 itself causes tissue damage, infection of enterocytes, and changes in intestinal haemostasis. Second, there is an intense release of inflammatory cytokines and dysregulation of the immune system. Thirdly, invasive medical procedures and prolonged hospital stays are associated with patient features and comorbidities (such as chronic obstructive pulmonary disease (COPD), diabetes, chronic renal failure, and immunosuppression). Additionally, the pandemic crisis led to overworked medical staff.[5]

Among hundreds of published articles with clinical data, only a few report secondary infections—mostly without detailed pathogens. Even in studies for which data on secondary infection were available, the rate of antibiotic use (94%-100%) was much higher than the reported incidence of secondary infection (10%-15%). In addition, most current infection control protocols aim to prevent transmission and cross-infection of SARS-CoV-2 without considering the prevention of secondary bacterial or fungal infection.[4]

Researchers are interested in studying co-infections, particularly bacterial and fungal infections in COVID-19, their correlation with the duration of

hospitalization, and clinical outcomes considering the facts.

METHOD

A retrospective cohort study was conducted on patients with severe or critical confirmed COVID-19 cases who were hospitalized in the COVID-19 Intensive Care Unit of RSUD Dr. Saiful Anwar Malang. Ethical clearance has been approved by the ethics committee with the number 400/165/K.3/302/2021.

Inclusion criteria in this study were patients who underwent sputum, blood, or urine culture examination; patients over 18 years old; patients with complete data on sputum culture results and/or blood and/or urine, and laboratory data of leukocytes, neutrophils, C-Reactive Protein (CRP) and procalcitonin. Patients who died before sputum, blood, or urine cultures were performed, as well as those with incomplete medical records, were excluded from the study.

According to the formula, the minimum number of samples was 76 people. In this study, 352 subjects who met the inclusion and exclusion criteria were taken data including data on the history of the course of the disease, epidemiological data, clinical data, supporting examination data both laboratory and radiology from the patient's medical record. Receiver Operating Characteristic (ROC) curve was used to determine the cut-off value of leukocytes, neutrophils, CRP and procalcitonin variables in determining the risk of coinfection.

The data was analysed and processed using IBM SPSS software version 26.0. Numerical data are reported by the mean and standard deviation. Categorical data are reported by percentage. The Kruskal-Walis test was used for analysis of variables and statistical significance was set at $P<0.05$.

RESULT

A total of 352 patients treated in the intensive care unit of Dr. Saiful Anwar Malang from August 2020 to August 2021 met the inclusion and exclusion criteria.

Table 1. Demographic Profile of Research Subjects

Variables	n	%
Age (mean±SD)	53.71±13.9	
Sex		
Male	117	33.2
Female	235	66.8
Co-infection		
Non-Coinfected	274	77.8
Coinfected with other microorganisms	78	22.2
Coinfected with		
Bacterial	66	84.61
Fungal	9	11.53
Fungal and bacterial	3	3.84

In the univariate analysis (Table 1), the mean age of the 352 COVID-19 patients was 53.71 years, with the youngest patient being 21 years old and the oldest being 88 years old. As many as 117 subjects (33.2%) were male and 235 subjects (66.8%) were female.

There were 274 (77.84%) non-coinfected subjects and 78 (22.15%) coinfected subjects out of a total of 352 subjects that matched the inclusion criteria. Out of them, 66 (84.61%) subjects had

bacterial coinfection, nine (11.53%) had fungal coinfection, and three (3.84%) had both bacterial and fungal coinfection.

Overall, there were 105 pathogens found in 78 co-infected patients. Ninety-three (88.57%) of them were bacteria—majorly accounted with gram-negative bacteria (70; 66.66%), followed by gram-positive bacteria (23; 21.90%)—and the remaining 12 (11.42%) were fungi. The most common pathogens identified were *Acinetobacter baumannii* (25), *Klebsiella pneumoniae* (21), and *Enterococcus faecalis* (15). *Candida glabrata* (4/3.80%) was found in most fungal infections, followed by *Candida albicans* (4/3.80%), *Candida tropicalis* (3/2.87%), and *Candida lusitaniae* (1/0.95%).

The test showed a significant difference in neutrophil counts between individuals with COVID-19 who were not coinfected and those who were coinfected, with patients in the coinfected group having median neutrophil counts that were generally higher (median=91.4%) than those in the non-coinfected group (median=82.85%).

The comparison of CRP in COVID-19 patients between the non-coinfected and coinfected groups revealed a significant value of P=0.001. The test revealed a significant difference in CRP levels between the coinfected and non-coinfected groups of COVID-19 patients, with the coinfected group's median CRP tending to be higher (median=10.06 g/mL) than the non-coinfected group's (median=7.26 g/mL).

The comparison of Procalcitonin in COVID-19 patients between the non-coinfected and coinfected groups showed a significance value (P<0.000), which indicated that Procalcitonin in COVID-19 patients between the non-coinfected and coinfected groups had quite difference in medians, where the median Procalcitonin in the coinfected group (median=0.655 ng/ml) tended to be higher than in the non-coinfected group (median=0.3 ng/ml).

Table 2. Correlation of Leukocyte, Neutrophil, CRP, and Procalcitonin Values with Co-infection in COVID-19 in Spearman Correlation Test

		Correlation	Coefficient Correlation	P
Leu	with	Co-infection	0.356	0.0001
Neutrophil	with	Co-infection	0.438	0.0001
CRP	with	Co-infection	0.187	0.001
Procalcitonin	with	Co-infection	0.221	0.0001
Leu	with	Bacterial co-infection	0.354	0.0001
Neutrophil	with	Bacterial co-infection	0.410	0.0001
CRP	with	Bacterial co-infection	0.164	0.003
Procalcitonin	with	Bacterial co-infection	0.192	0.0001
Leu	with	Fungal co-infection	0.028	0.596
Neutrophil	with	Fungal co-infection	0.096	0.074
CRP	with	Fungal co-infection	0.090	0.105
Procalcitonin	with	Fungal co-infection	0.122	0.024
Leu	with	Bacterial and fungal co-infection	0.057	0.290
Neutrophil	with	Bacterial and fungal co-infection	0.071	0.184
CRP	with	Bacterial and fungal co-infection	-0.009	0.876
Procalcitonin	with	Bacterial and fungal co-infection	-0.026	0.630

The tests were followed with a correlation test of the leukocyte, neutrophil, CRP, and procalcitonin levels in COVID-19 coinfection. There are positive correlation results between Leukocytes and Co-infection (P=0.0001), Leukocytes and Bacterial co-infection (P=0.0001), Neutrophils and co-infection (P=0.0001), Neutrophils and bacterial co-infection (P=0.0001), CRP and coinfection (P=0.001), CRP and bacterial co-infection (P=0.003), Procalcitonin and coinfection (P=0.000), Procalcitonin and bacterial co-infection (P=0.0001), Procalcitonin and fungal co-infection (P=0.024).

It indicates that with the higher the leukocytes level, co-infection and bacterial co-infection will be more severe, with the higher the neutrophils level, co-infection and bacterial co-infection will be more severe, with the higher the CRP level, co-infection and bacterial co-infection will be more severe, with the higher the procalcitonin level, co-infection, bacterial co-infection, and fungal co-infection will be more severe.

The study was followed with chi-square test in which was found significant correlation between leukocytes (a category based on the cut-off value of ROC) and coinfection (P=0.0001), neutrophils (a category based on the cut-off value of ROC) and coinfection (P=0.0001), but no significant correlation between neutrophils (a category based on the cut-off value of ROC) and coinfection (P=0.064). The following diagnostic value was thus obtained based on the crosstabs (Table 3).

Table 3. Threshold Values for Leukocytes, Neutrophils, CRP, and Procalcitonin with Coinfection in COVID-19

Values	Coinfected	Non-Coinfected	P
Leu (with ROC cut-off)			
>12485	53 (67.9%)	90 (32.8%)	0.0001
<12485	25 (32.1%)	184 (67.2%)	
Neutrophil (with ROC cut-off)			
>88.2	56 (71.8%)	76 (27.7%)	0.0001
<88.2	22 (28.2%)	198 (72.3%)	
CRP (with ROC cut-off)			
>8.74	46 (59.0%)	129 (47.1%)	0.064
<8.74	32 (41.0%)	145 (52.9%)	
Procalcitonin (with ROC cut-off)			
>19.73	6 (7.7%)	17 (6.2%)	0.639
<19.73	72 (92.3%)	257 (93.8%)	

With a sensitivity value of 71.8%, neutrophils were found to have the greatest sensitivity compared to leukocytes, CRP, and procalcitonin. However, the results of the specificity test showed that the Procalcitonin marker had the highest specificity value of 93.8%, followed by neutrophils at 72.3%, leukocytes with a specificity of 67.2%, and CRP markers with a specificity of 52.9%.

Table 4. Diagnostic Value of Leukocytes, Neutrophils, CRP, and Procalcitonin with Coinfection in COVID-19

Characteristics	Sensitivity	Specificity	PPV	NPV	PPR	Accuray	OR
Leu	67.9%	67.2%	37.1%	88.0%	2.069	67.3%	4.334
Neutrophil	71.8%	72.3%	42.4%	90.0%	2.588	72.2%	6.632
CRP	59.0%	52.9%	26.3%	81.9%	1.253	54.3%	1.616
Procalcitonin	15.8%	93.8%	26.1%	88.9%	2.545	84.3%	2.835

Note: NPV=Negative predictive value; PPV=Positive predictive value; PPR=Positive probability ratio; OR=Odds Ratio

Additionally, as shown in the table above, the positive predictive value (PPV)—i.e., the probability of the subject being co-infected if the result of the diagnostic test is positive—for neutrophils—which is 42.4%—is the highest compared to other test parameters. This indicates that if the diagnostic test results are positive, the person is more likely to be co-infected.

Meanwhile the negative predictive value (NPV)—the probability of the subjects being not coinfected if the results of the diagnostic test are negative—showed the Neutrophil marker as the highest value—which is 90.0%—followed by Procalcitonin at 88.9%, Leukocytes at 88.0%, and the last is CRP, at 81.9%. The probability ratio (LR)—the probability of co-infected subjects getting a positive diagnostic test result—among the 4 markers showed that sequentially, the largest is the Neutrophil—which is 2,588—and Procalcitonin—2,545, followed by Leukocytes with a value of 2,069, and CRP with a value of 1,253.

The prediction accuracy in estimating the possibility of the subjects labelled as non-coinfected or coinfected based on Leukocyte biomarkers is 67.3%. Given the odds ratio of 4.334 (OR>1), it can be inferred that the leukocytes could be a risk factor in determining the status of coinfection, wherein a leukocyte of greater than 12.485, may indicates that the patient has a 4.33 times risk of co-infection compared to patients with Leukocytes value of less than 12485.

As shown in the table above, neutrophils, CRP, and procalcitonin could be risk factors in determining the coinfection status. A neutrophil value of greater than 88.2 may indicate that the patient has a 6.632 times risk of co-infection compared to patients with a neutrophil value of less than 88.2. A CRP value greater than 8.74 may indicate that the patient has a 1.616 times risk of co-infection compared to patients with a CRP value of less than 8.74. A procalcitonin value of greater than 19.73 may indicate that the patient has a 1.260 times risk of co-infection compared to patients with a Procalcitonin value of less than 19.73

The length of hospitalization of non-coinfected patients had a mean value of 6,38 days, less than that of coinfected patients, who had a mean value of 13,47 days.

Table 5. The Correlation between LoH and Coinfection

	LoH (days)	
	Coefficient Correlation	**P**
Bacteria/Fungi	0.382	1.000*

Note: LoH=Length of Hospitalization;
*Spearman correlation test

We could determine a significant correlation between length of hospitalization (LoH) and coinfection status and conclude a significant correlation between LoH and bacterial/fungal (non-coinfection, bacterial, fungal, and fungal + bacteria coinfection). In this study, we found that of 274 non-coinfected patients, 31% died and 69.0% were discharged. Meanwhile, of 78 coinfected patients, 71.8% died and 28.2% were discharged.

Using the Spearman correlation test between the clinical outcomes of patients with coinfection (non-coinfected and

coinfected), we found a significant relationship between the prognosis and coinfected status of the subjects. In other words, co-infection increases the mortality risk in a patient.

In this study, we found that of 274 non-coinfected patients, 31% died, while 69.0% were discharged. Meanwhile, of the 66 patients with bacterial co-infection, 71.2% died and 28.8% were discharged. Of the 9 patients with fungal co-infection, 88.9% died and 11.1% were discharged. As for the 3 patients with fungal + bacterial coinfection, 33.3% died and 66.7% were discharged. There is a significant correlation between patient outcomes and bacteria/fungi (non-coinfection, bacterial, fungal, and fungal + bacterial coinfection). In other words, the presence of bacterial/fungal co-infection (non-coinfection, bacterial coinfection, fungi, and fungal + bacterial coinfection) in patients increases the mortality risk.

DISCUSSION

There were 78 coinfected COVID-19 patients (22.15%) compared to 274 non-coinfected patients (77.85%), with 66 (18,75%) being a bacterial coinfection, nine (2,55%) having a fungal coinfection, and three (0,85%) having both bacterial and fungal coinfection. Previously conducted studies showed varying results of the percentage of coinfection in COVID-19. According to Zhang et al, the percentage of bacterial coinfection in COVID-19 was 7.7% and fungal coinfection was 3.3%. Zhang et al stated that COVID-19 with higher severity had a higher percentage of coinfection—25.5% being bacterial and 10.9% being fungal.[6] This aligns with a study in France, which stated that the percentage of coinfection in COVID-19 patients in the ICU was 19.8%—the among being almost the same as we found in this study.[7]

The median age value in the two groups did not differ, both being 56 years. Oxidation and inflammation processes will increase with age.[8] This could be one of the factors influencing clinical outcomes in COVID-19 infection. However, in this study, we found the median age between the non-coinfected and coinfected groups are the same, thus indicating no statistical difference between the ages of the two groups.

The number of female samples was more than the number of male samples in the two study groups—66.4% against 33.6% in the non-coinfected group and 67.9% against 32.1% in the coinfected group. This contradicts earlier studies that claimed COVID-19 affected men more than women. However, the mechanism that influences this difference is not clear. However, there was no statistically significant difference in terms of gender in the coinfected and non-coinfected groups in this study (P=0.801).[9]

There are no significant characteristics of comorbidities in the two groups—60.6% being non-coinfected and 64.1% being coinfected. A meta-analysis study states that comorbidities increase the severity of COVID-19.[10] Another meta-analysis study conducted in Iran stated that

comorbidities, especially diabetes and hypertension, increase the risk of severity and the possibility of ICU admission up to two times, and cardio-cerebrovascular-related comorbidities could increase it three times.[11] Comorbidities were not confounding factors in this study, as their prevalence did not significantly differ between the two groups.

Gram-negative bacteria made up most of the pathogens in the COVID-19 coinfected group (66.66%), followed by gram-positive bacteria (21.90%) and fungi (11.42%), with *Acinetobacter baumanii* (25), *Klebsiella pneumoniae* (21), and *Enterococcus faecalis* (15) being the most prevalent pathogens. *Candida albicans* (4), *Candida glabrata* (4), and *Candida tropicalis* (3) are the most prevalent fungal pathogens. The characteristics of this pathogen are almost the same as the multicentre cohort study conducted in China with the most pathogens being gram-negative bacteria (50%), followed by gram-positive bacteria (26.92%), viruses (11.54%) and fungi (7,69%) with the most common pathogens being Klebsiella pneumoniae, Enterococcus faecium, Acinetobacter baumannii.[6]

Leukocytes in the coinfected group had a significantly higher value than the non-coinfected group ($P<0.05$). There was also a significant correlation ($r=0.356$, $P=0.0001$) between leukocytes and the presence of coinfection.in line with a prior study by Lv et al, which found that COVID-19 coinfection resulted in considerably greater leukocyte values than non-coinfection.[9]

A study by Silva et al also stated that leukocytes would increase significantly in coinfected COVID-19 patients compared to non-coinfected patients ($P<0.001$).[12] Increased leukocyte values can be caused by infection. The leukocyte value may decrease at the beginning of a severe infection but may increase later on.[13]

This study found significantly higher neutrophil counts in coinfected patients compared to non-coinfected ones. Previous research also indicates that neutrophil levels remain elevated in co-infected COVID-19 patients, even after antibiotic treatment.[14] Our findings confirm that neutrophil count correlates with bacterial coinfection but not with fungal or mixed infections. This aligns with Mason et al, who reported a similar increase in neutrophil levels in bacterial coinfection.[15]

C-Reactive Protein, as a systematic marker for inflammation and tissue damage, is extensively used by clinicians to monitor infections. In this study, we found that CRP had a significant correlation with coinfection status in COVID-19. According to a study by Lv et al, the CRP value in the coinfected group was noticeably greater than the non-coinfected group.[9]

In this study, we also found a significant correlation between CRP values and bacterial coinfection. However, there was no significant correlation between CRP values and either fungal coinfection or a combination of both bacterial and fungal coinfection. This is in accordance with a study by Wang et al who found a significant difference between the CRP values in the

bacterial coinfected and non-coinfected group (P<0.05).[16]

Procalcitonin production is triggered by bacterial toxins and inflammatory cytokines, whose activation and production is inhibited by the large amount of INF-γ produced during viral infection. It is in alignment with our study that procalcitonin levels have a significant correlation with coinfection in COVID-19 infection. A study by Tang et al suggested that in COVID-19 with coinfection, procalcitonin values were found higher than without, which was due to a greater inflammatory response in coinfected rather than non-coinfected patients.[17]

In this study, the average length of hospitalization (LoH) for non-coinfected patients was 6,3773 days and for coinfected patients, it was 13,4675 days. Additionally, there was a strong correlation between the LoH and coinfection status. Coinfection leads to hematological and biochemical imbalances, worsening the general condition and prolonging hospital stay. This is in accordance with a study by Silva et al which stated that coinfection would lead to a longer length of hospitalization and increase the cost of care for COVID-19 patients compared to the non-coinfected group.[12]

A study by Signorini et al, stated that coinfection would lead to a longer LoH in ICU than patients without coinfection (median 15 days vs. 5 days).[18] A study by Zhang et al found that patients without co-infection with COVID-19 had a higher chance of being hospitalized in under 60 days than co-infected patients (P<0.001).[6]

In this study, the mortality rate in the non-coinfected patient was 31%, and 71.8% in the coinfected patient. A significant correlation was found between COVID-19 infection and clinical outcomes. This is in accordance with a study by Silva et al , which stated that coinfection would lead to a longer length of hospitalization and increase the cost of care for COVID-19 patients compared to the non-coinfected group.[12]

Based on a study by Signorini et al, the presence of coinfection will increase the mortality rate within 28 days than in the patients without coinfection (P<0.001). If the mortality rate is differentiated between bacterial coinfection and fungal coinfection, there is a significant increase in mortality rate in bacterial coinfection but not in fungal coinfection.[18] A study by Costa et al stated that coinfection would lead to an increased risk of death in COVID-19 patients compared to the non-coinfected group.[19]

This study has some limitations as it was conducted in a single centre and because of its retrospective nature, data availability was limited to the medical records of the hospital. Other factors, such as standard therapy, disease severity, comorbidities, and mechanical ventilation, may still affect outcomes.

CONCLUSION

In this study, we found a significant increase in leukocyte values, neutrophil values, procalcitonin values, and length of hospitalization in COVID-19 patients with

coinfection. Moreover, there was a significantly higher mortality rate in COVID-19 patients with coinfections.

REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507–13.
2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91(1):157–60.
3. Wang L, Amin AK, Khanna P, Aali A, McGregor A, Bassett P, et al. An observational cohort study of bacterial co-infection and implications for empirical antibiotic therapy in patients presenting with COVID-19 to hospitals in North West London. Journal of Antimicrobial Chemotherapy. 2021;76(3):796–803.
4. Zhou P, Liu Z, Chen Y, Xiao Y, Huang X, Fan XG. Bacterial and fungal infections in COVID-19 patients: A matter of concern. Infect Control Hosp Epidemiol. 2020;41(9):1124–5.
5. Nebreda-Mayoral T, Miguel-Gómez MA, March-Rosselló GA, Puente-Fuertes L, Cantón-Benito E, Martínez-García AM, et al. Bacterial/fungal infection in hospitalized patients with COVID-19 in a tertiary hospital in the Community of Castilla y León, Spain. Enfermedades infecciosas y microbiologia clinica (English ed). 2022;40(4):158–65.
6. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, et al. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect. 2020;9(1):1958–64.
7. Elabbadi A, Turpin M, Gerotziafas GT, Teulier M, Voiriot G, Fartoukh M. Bacterial coinfection in critically ill COVID-19 patients with severe pneumonia. Infection. 2021;49(3):559–62.
8. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25:1822–32.
9. Lv Z, Cheng S, Le J, Huang J, Feng L, Zhang B, et al. Clinical characteristics and co-infections of 354 hospitalized patients with COVID-19 in Wuhan, China: a retrospective cohort study. Microbes Infect. 2020;22(4–5):195–9.
10. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2:1069–76.
11. Honardoost M, Janani L, Aghili R, Emami Z, Khamseh ME. The Association between Presence of Comorbidities and COVID-19 Severity: A Systematic Review and Meta-Analysis. Cerebrovascular Diseases. 2021;50(2):132–40.
12. Silva DL, Lima CM, Magalhães VCR, Baltazar LM, Peres NTA, Caligiorne

RB, et al. Fungal and bacterial coinfections increase mortality of severely ill COVID-19 patients. Journal of Hospital Infection. 2021;113:145–54.

13. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. International Journal of Infectious Diseases. 2020;95:332–9.
14. Cambier S, Metzemaekers M, de Carvalho AC, Nooyens A, Jacobs C, Vanderbeke L, et al. Atypical response to bacterial coinfection and persistent neutrophilic bronchoalveolar inflammation distinguish critical COVID-19 from influenza. JCI Insight. 2022;7(1):e155055.
15. Mason CY, Kanitkar T, Richardson CJ, Lanzman M, Stone Z, Mahungu T, et al. Exclusion of bacterial co-infection in COVID-19 using baseline inflammatory markers and their response to antibiotics. Journal of Antimicrobial Chemotherapy. 2021;76(5):1323–31.
16. Carbonell R, Urgelés S, Salgado M, Rodríguez A, Reyes LF, Fuentes Y V., et al. Negative predictive value of procalcitonin to rule out bacterial respiratory co-infection in critical covid-19 patients. Journal of Infection. 2022;85(4):374–81.
17. Tang ML, Li YQ, Chen X, Lin H, Jiang ZC, Gu DL, et al. Co-Infection with Common Respiratory Pathogens and SARS-CoV-2 in Patients with COVID-19 Pneumonia and Laboratory Biochemistry Findings: A Retrospective Cross-Sectional Study of 78 Patients from a Single Center in China. Medical Science Monitor. 2021;27:e929783.
18. Signorini L, Moioli G, Calza S, Van Hauwermeiren E, Lorenzotti S, Del Fabro G, et al. Epidemiological and Clinical Characterization of Superinfections in Critically Ill Coronavirus Disease 2019 Patients. Crit Care Explor. 2021;3(6):e0430.
19. da Costa RL, Lamas C da C, Simvoulidis LFN, Espanha CA, Moreira LPM, Bonancim RAB, et al. Secondary infections in a cohort of patients with COVID-19 admitted to an intensive care unit: impact of gram-negative bacterial resistance. Rev Inst Med Trop Sao Paulo. 2022;64:e6.

Original Article

Effect of Body Mass Index, Sputum Conversion Status, and Adverse Drug Events Severity On Health-Related Quality of Life of Drug-Resistant Tuberculosis Patients

Sandy Kurniawan*, Jatu Aphridasari, A Farih Raharjo

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, dr. Moewardi General Hospital, Surakarta

Corresponding Author:
Sandy Kurniawan | Department of Pulmonary and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, dr. Moewardi General Hospital, Surakarta | sandy.kurniawan.md@gmail.com

Submitted: January 15th, 2024
Accepted: March 7th, 2025
Published: March 8th, 2025

Respir Sci. 2025; 5(2): 72-81
https://doi.org/10.36497/respirsci.v5i2.168

Abstract

Background: Adherence to treatment guidelines and bacteriological conversion are the main indicators of successful treatment of drug-resistant tuberculosis patients. Evaluation of health-related quality of life (HRQoL) and the effect of treatment on HRQoL are often ignored. HRQoL assessment is an interesting outcome to evaluate and improve. Drug-resistant tuberculosis patients suffer not only from the disease but also from the effects of the treatment.

Method: This study used a cross-sectional design to determine the correlation of body mass index (BMI), sputum conversion status, and adverse drug events severity with the HRQoL of drug-resistant tuberculosis patients. Quality of life assessment using the WHOQol-BREf questionnaire. The study was conducted in October 2022 at dr. Moewardi Hospital, Surakarta and Dr. Ario Wirawan, Salatiga. Determination of the sample by total sampling method.

Results: HRQoL in 33 study subjects ie, 15 subjects had good HRQoL and 18 subjects had poor HRQoL. The media for each quality of life domain are the physical domain 43.00±6.20, psychological domain 33.21±8.83, social domain 28.21±11.01, and environmental domain 33.45±6.38. Statistical analysis with rank Spearman showed that there were a relationship between BMI (P=0.018), sputum conversion status (P=0.002), and adverse drug events severity (P=0.0001) with HRQoL of drug-resistant tuberculosis patients.

Conclusion: BMI, sputum conversion status, and drug adverse events severity affect HRQoL of drug-resistant tuberculosis patients.

Keywords: drug-resistant tuberculosis, HRQoL

INTRODUCTION

The tuberculosis (TB) control program is aimed at optimizing microbiological cures and using microbiological parameters as indicators of treatment success. Although this is highly important from a public health perspective, such an approach does not adequately address the physical, mental, and social suffering of patients caused by TB. Patients

suffer not only from the symptoms of the disease but also from a general decline in their quality of life. Patients' perceptions of their illness and health remain largely unexplored.[1,2]

Quality of life is a broad and complex multidimensional concept that encompasses physical, social, psychological, economic, and spiritual domains. It is difficult to define and measure but can be broadly described as an individual's perception of their position in life within the context of the culture and value systems in which they live and concerning their goals, expectations, standards, and concerns. Quality of life is more an expression of the preferences and values of patients rather than a judgment made by physicians.[3,4]

Studies on health-related quality of life (HRQoL) of drug-resistant tuberculosis (DR-TB) patients undergoing treatment with anti-TB drugs are still limited. Research on the factors influencing the quality of life of drug-resistant TB patients will provide new insights into the management of these patients. The author aims to investigate the HRQoL of DR-TB patients receiving treatment, as well as the correlation between body mass index (BMI), sputum conversion status, and the severity of adverse drug events with the quality of life of these patients.

METHOD

This study employed a cross-sectional design and was conducted in October 2022 at the MDR-TB clinics of dr. Moewardi Hospital, Surakarta and dr. Ario Wirawan Hospital, Salatiga. The target population consisted of DR-TB patients undergoing treatment at these facilities during the study period. The accessible population included all DR-TB patients registered at the PMDT clinics of the aforementioned hospitals in October 2022.

The research sample was selected using consecutive sampling, whereby all eligible subjects meeting predefined criteria were included. Inclusion criteria comprised DR-TB patients aged 18 years or older who were within the first to sixth months of treatment and provided written informed consent to participate in the study. Exclusion criteria included incomplete medical record data relevant to the study and DR-TB patients with pre-existing conditions before treatment initiation, such as anemia, gout arthritis, cardiac arrhythmias, hearing impairment, mental disorders, hepatitis, or chronic kidney failure.

HRQoL was assessed using the WHOQoL-BREF questionnaire. A total score of <60 was classified as a "poor" quality of life, while a score of ≥60 was classified as "good." The WHOQoL-BREF instrument also evaluates four distinct domains of quality of life: physical, psychological, social, and environmental.

This study received ethical approval from the Ethical Review Committee of Dr. Moewardi Hospital on October 7, 2022 (approval number: 1.028/X/HREC/2022). All procedures adhered to ethical standards for research involving human subjects.

Data were analyzed using SPSS 21 for Windows. The primary objective of this study was to examine the relationship between HRQoL and factors such as body mass index (BMI), sputum conversion status, and the severity of adverse drug events. The Spearman's rank correlation test was used to assess the association between independent and dependent variables. A value of P<0.05 was considered statistically significant, and the strength of the correlation was determined by the r-value.

RESULT

The subjects of this study were 33 DR-TB patients undergoing treatment and fulfilling the inclusion and exclusion criteria at dr. Moewardi Hospital and dr. Ario Wirawan Hospital. The characteristics of the research subjects are presented in Table 1.

Table 1. Subject characteristic

Characteristic	n	%
Sex		
Male	25	75.8%
Female	8	24.2%
Age		
18 - 39	10	30.3%
40 – 60	17	51.5%
>60	6	18.2%
Education		
Bachelor	1	3.3%
Senior high school	12	36.1%
Junior high school	15	45.5%
Elementary school	3	9.1%
No education	2	6.1%
Employment status		
Employed	12	36.4%
Unemployed	21	63.6%
BMI (Mean±SD; Min-max)	20.00±2.81	13.82-25.81

Most subjects were men (75.8%) in their productive age. Most of the education levels are junior and high school, which shows that education plays a role in understanding TB disease and its treatment.

Table 2. HRQoL of DR-TB patients

HRQoL	n (%)
Good (score ≥60)	15 (45.45%)
Poor (score <60)	18 (54.55%)

The quality of life assessment indicates that 54.55% of patients experience a diminished quality of life. The physical, psychological, social, and environmental categories exhibited low ratings, signifying that patients encountered a substantial effect of the disease and therapy on their quality of life. Meanwhile, Table 3 displays the score for the assessment of HRQoL.

Table 3. HRQoL of DR-TB patients

HRQoL Domain	Score
Physique	43.00±6.20
Psychological	33.21±8.83
Social	28.21±11.01
Environment	33.45±6.38

The study found that there was a moderate relationship between BMI and HRQoL, with the value of P=0.018. This shows that patients with a better BMI tend to have a better quality of life. The statistical test for the relationship between BMI and HRQoL of DR-TB patients is shown in Table 4.

Table 4. Relationship between BMI and HRQoL in DR-TB patients

Variable	HRQoL	
	R	P
BMI	0.409	0.018*

Note: Spearman rank test; *) Significant at α=5%

Table 5. Relationship between sputum conversion status and adverse events (Aes) severity with HRQoL in DR TB patients

Variable	HRQoL		P	r
	Poor	Good		
Sputum Conversion Status				
Not yet converted	15 (45.45%)	5 (15.15%)	0.002*	0.510
Converted	3 (9.09%)	10 (30.30%)		
AEs severity				
No AEs	3 (9.09%)	9 (27.27%)		
Mild	5 (15.15%)	6 (18.18%)		
Moderate	6 (18.18%)	0 (0.00%)	0.0005*	-0.594
Severe	4 (12.12%)	0 (0.00%)		
Life-threatening	0 (0.00%)	0 (0.00%)		

Note: Spearman rank test. *) Significant at α=5%

A weak correlation exists between sputum conversion status and HRQoL (P=0.002), indicating that patients who have undergone sputum conversion exhibit superior quality of life compared to those who have not. Adverse drug effects were observed in 21 patients (63.64%). The findings indicate a moderate and substantial correlation between the intensity of pharmacological side effects and HRQoL (P=0.0005), with individuals experiencing milder side effects reporting a superior quality of life. Table 5 presents the statistical analysis of the correlation between sputum conversion status and the severity of adverse drug events with HRQoL in DR-TB patients.

DISCUSSION

Assessing the quality of life in patients with chronic illnesses, such as tuberculosis, is a critical responsibility for healthcare personnel. The extended duration of treatment and the necessity for compliance substantially impact mental and social well-being. Numerous research indicates that assessing patients' quality of life functions as a criterion for the quality of healthcare services. Assessing a patient's quality of life helps provide a standard for enhancing therapy and health services.[4,5]

Quality of life is defined as an individual's evaluation of physical and mental well-being and its impact on physical, psychological, economic, spiritual, and social-relational functions. The assessment of quality of life elucidates the patient's condition in relation to their illness and its impact on personal functioning and everyday activities.[4,5]

The male proportion is 75.8%, surpassing the female proportion of 24.2% in this study. The findings of this study align with those of Widyasrini et al, which indicated that the proportion of male DR-TB patients was 57.7%, and Kurniawan et al, which reported a proportion of 63.4% of male DR-TB patients. Gender influences mycobacterial exposure through variations in social roles, risk behaviors, and activities. Men may engage in more frequent travel, maintain a greater number of social connections, and participate in occupations linked to an elevated risk of tuberculosis. Moreover, there is evidence of physiologic

disparities between genders that may influence susceptibility to mycobacterial infection.[6–9]

Animal studies have shown that male C57BL/6 mice have a lower ability to control *Mycobacterium tuberculosis* (*M. tuberculosis*) infection than female mice. This is due to less effective innate and adaptive immune responses, characterized by higher bacterial loads in the lungs and faster mortality. Differences in the early stages of the innate immune response also influence the level of bacterial load and the subsequent development of the adaptive immune response.[6–9]

Pathogen recognition and inflammatory and antimicrobial responses also differ between male and female mice, with genetic and hormonal factors playing important roles. Estrogen is known to enhance the ability of macrophages to kill bacteria such as *Streptococcus pneumoniae*, while peritoneal macrophages from female mice show stronger antimicrobial activity against *Mycobacterium* intracellulare than male mice.[6–9]

IFNγ is an important cytokine produced by CD4+ and CD8+ T cells that plays a role in enhancing the antibacterial function of macrophages. Invariant Natural Killer T (iNKT) cells, which act as a link between innate and adaptive immunity, can recognize *M. tuberculosis*-infected macrophages, produce IFNγ, and kill intracellular bacteria. Estradiol has also been shown to increase IFNγ production by iNKT cells in female mice.[6–9]

Castration or removal of the estradiol receptor reduces IFNγ production, which can be restored by estradiol injection. Testosterone has anti-inflammatory effects by inhibiting pro-inflammatory factors such as TNF-α and increasing IL-10 production. Castration of male mice increases TNF-α secretion, and TB susceptibility can be reduced by castration, suggesting that testosterone may be a factor that increases TB susceptibility. Female mice exhibit higher T cell activity, including the production of Th1-type cytokines such as IFNγ, as well as stronger antibody responses than male mice.[6–9]

These differences in adaptive immunity may contribute to the inability of male mice to control *M. tuberculosis* infection over the long term. In addition to hormonal factors, sex differences in TB are also influenced by genetic factors, such as the expression of immunity-related genes on the X chromosome and the advantage of genetic diversity in female mice due to cellular mosaicism and genes that escape X chromosome inactivation. Thus, the difference in susceptibility to TB between male and female mice is the result of a complex interaction between hormonal and genetic factors.[6–9]

The majority of patients in this study were of productive age. A study by Abrori et al reported that DR-TB patients in Banyumas, Indonesia mostly occurred in adolescents and adults. A study by Dela et al reported that DR-TB in India was found in the majority at the age of 21-60 years. High mobility and higher social interaction

are the causes of the high incidence of DR-TB cases in this age range.[10,11]

The educational level of the patients in this study mostly had lower secondary education. This research is in line with the research of Abrori et al and Bawoente et al. Level of education is a risk factor for tuberculosis transmission. Education level is related to knowledge and understanding of tuberculosis prevention. The level of education is also related to knowledge about homes and environments that meet health requirements. Someone with a good level of knowledge tends to develop a clean and healthy lifestyle.[11,12]

DR-TB patients in this study mostly had poor quality of life. The HRQoL of DR-TB patients in this study consisted of 15 patients (45.54%) with good quality of life and 18 patients (54.55%) with poor quality of life. The HRQoL of patients in this study is in line with the studies of Dhelaimi et al and Jaber et al. HRQoL is defined as the extent to which a patient's subjective perception of physical, mental and social well-being is affected by the disease and its treatment every day. The need to assess quality of life becomes important because of the broader concept of measuring health status beyond conventional indicators such as mortality and morbidity. HRQoL is an indicator of the effects of disease and morbidity on daily activities and functions.[13,14]

Malnutrition and TB are major problems in almost all developing countries in the world. Both tend to interact with each other. Poor nutritional status will affect the body's defense system which causes an individual to be more susceptible to infection with a disease. Tuberculosis also causes metabolic changes in the body where there is an increase in metabolism as a response to the body's infection so that there is a decrease in appetite, malabsorption of macro and micro-nutrients, a decrease in fat-free mass, and fat mass which ultimately increases morbidity and mortality rates.[15–17]

In conditions of infection, there is an increase in metabolism which uses the protein as an energy source to fight pathogenic germs, causing degradation of muscle protein and a decrease in protein in the blood circulation. Selection of protein types that contain complete amino acids also called high-quality protein and are easily digested by the body are the main choices in determining the type of protein to be consumed because it affects its ability to be used immediately by the body and is beneficial for preventing a decrease in fat-free mass in the body which ultimately improves the quality of life of TB patients.[15,16]

Sputum conversion plays an important role in determining DR-TB treatment and indicators of treatment effectiveness. Sputum that does not convert or is late in converting until the end of 4 months of intensive phase treatment often indicates unfavorable outcomes such as treatment failure and death. Late sputum conversion has negative impacts such as prolonging the therapy period and less than optimal treatment compliance with the consequences of treatment failure. Sputum conversion in DR-TB patients in

79.5% of patients occurred in the first two months of treatment. Sputum conversion indicates treatment effectiveness, reduced risk of TB transmission to others, improvement in clinical symptoms, and improved quality of life of patients.[18,19]

This study identified the impact of sputum conversion status on HRQoL in DR-TB patients. These findings align with the research conducted by Dar et al. The research conducted by Dar et al analyzed the HRQoL of tuberculosis patients at the onset of treatment and following the completion of the intense phase. The research indicated enhancements in HRQoL during the intensive phase of tuberculosis medication. The dimensions of quality of life that underwent the most significant enhancement were the physical and psychological domains.[20,21]

Enhancements in the physical aspect of quality of life were associated with the amelioration of tuberculosis symptoms following the completion of the intense treatment period. A subsequent investigation by Dujaili et al yielded analogous findings. The research conducted by Dujaili et al indicated that enhancements in physical well-being, functional well-being, and overall quality of life ratings were observed following the completion of the intense phase of anti-tuberculosis therapy.[20,21]

The treatment for DR-TB requires a greater number of drug combinations compared to drug-sensitive tuberculosis, hence elevating the probability and intensity of AEs. The evaluation of adverse events is essential for decreasing morbidity and mortality associated with DR-TB. The majority of adverse events are minimal and can be managed without altering or discontinuing the prescription regimen. Severe pharmacological side effects can significantly jeopardize health, need hospitalization, or perhaps threaten life.[5,22]

The frequency of drug AEs in this study was 63.64%. The frequency of drugs AEs in this study is in line with a study by Ahmad et al in Pakistan at 72%, Nilamsari et al at 70% in Indonesia and Dela et al in India at 57.6%. Variations in the reported frequency of AEs may be due to differences in attitudes towards therapy such as lack of medication adherence, default rates, differences in opinion of patients and doctors regarding reporting of drugs AEs, differences in support programs, initial assessment, and management of drugs AEs.[11,23–25]

Tuberculosis significantly seriously affects patients' quality of life. The occurrence and severity of drug adverse events associated with DR-TB treatment are well-documented; nevertheless, the impact of these medication adverse events on patients' quality of life remains largely unexplored. The research by Dela et al indicated that the occurrence of drug adverse events diminished the HRQoL of DR-TB patients, and a correlation existed between HRQoL and adherence to treatment guidelines.[11,23]

The adverse effects of anti-tuberculosis medications, particularly second-line agents for drug-resistant tuberculosis, can profoundly affect a patient's quality of life through multiple

routes. Physically, adverse effects including anorexia, nausea, vomiting, visual disturbances, alterations in urine color, pruritus, erythema, and auditory impairment can diminish the patient's overall physical health, thereby restricting the capacity to engage in daily activities, reducing mobility, and inducing persistent discomfort.[24,26,27]

Moreover, these medications may adversely impact the patient's psychological condition, exacerbating mental health issues such as depression and, in extreme instances, potentially inducing hallucinations and a sense of hopelessness. The psychological and physical effects may diminish a patient's motivation to persist with therapy, resulting in non-compliance, which can subsequently impede recovery, elevate the risk of drug resistance, and exacerbate the overall state of tuberculosis. The absence of social support can exacerbate the deterioration of the quality of life for these individuals.[24,26,27]

CONCLUSION

The majority of DR-TB patients receiving anti-tuberculosis therapy exhibit diminished HRQoL. The body mass index, sputum conversion status, and severity of drug adverse events are correlated with the HRQoL of DR-TB patients. Substandard quality of life can influence treatment adherence in DR-TB patients. The treatment of DR-TB should prioritize not only patient healing but also the enhancement of patient quality of life.

REFERENCES

1. Brown J, Capocci S, Smith C, Morris S, Abubakar I, Lipman M. Health status and quality of life in tuberculosis. International Journal of Infectious Diseases. 2015;32:68–75.
2. Khan S, Tangiisuran B, Imtiaz A, Zainal H. Health Status and Quality of Life in Tuberculosis: Systematic Review of Study Design, Instruments, Measuring Properties and Outcomes. Health Science Journal. 2017;11(1):484.
3. Febi AR, Manu MK, Mohapatra AK, Praharaj SK, Guddattu V. Psychological stress and health-related quality of life among tuberculosis patients: a prospective cohort study. ERJ Open Res. 2021;7(3):00251–2021.
4. Rachmawati DS, Nursalam N, Hargono R, Otok BW. Quality of Life and Subjective Well-Being Modeling of Pulmonary Tuberculosis Patients. J Public Health Res. 2021;10(2):2180.
5. Salehitali S, Noorian K, Hafizi M, Dehkordi AH. Quality of life and its effective factors in tuberculosis patients receiving directly observed treatment short-course (DOTS). J Clin Tuberc Other Mycobact Dis. 2019;15:100093.
6. Widyasrini ER, Probandari AN, Reviono R. Factors Affecting the Success of Multi Drug Resistance (MDR-TB) Tuberculosis Treatment in Residential Surakarta. Journal of

Epidemiology and Public Health. 2017;02(01):45–57.
7. Kurniawan S, Reviono R, Sutanto YS. Pengaruh faktor usia, berat badan, dosis dan rejimen terhadap waktu timbulnya efek samping gastrointestinal, hepatotoksik, dan kesembuhan pada tuberkulosis resisten obat. Universitas Sebelas Maret. Surakarta: Universitas Sebelas Maret; 2020. p. 41–60.
8. Humayun M, Chirenda J, Ye W, Mukeredzi I, Mujuru HA, Yang Z. Effect of Gender on Clinical Presentation of Tuberculosis (TB) and Age-Specific Risk of TB, and TB-Human Immunodeficiency Virus Coinfection. Open Forum Infect Dis. 2022;9(10):ofac512.
9. Dutta NK, Schneider BE. Are There Sex-Specific Differences in Response to Adjunctive Host-Directed Therapies for Tuberculosis? Front Immunol. 2020;11:1465.
10. Abrori I, Ahmad RA. Gambaran Kualitas Hidup Penderita Tuberkulosis Resistan Obat dan Karakteristiknya di Kabupaten Banyumas, Provinsi Jawa Tengah, Periode Tahun. Berita Kedokteran Masyarakat. 2018;34(2):55–61.
11. Dela AI, Tank NKD, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: A four year retrospective study. Lung India. 2017;34(6):522–6.
12. Bawonte TG, Mambo CD, Masengi ASR. Faktor-Faktor Yang Mempengaruhi Tuberculosis Multidrug Resistance (TB MDR). eBiomedik. 2021;9(1):117–25.
13. Omar Dhelaimi G, Alsaedi TS, Alharbi MO, Alkaraiem F, Altarjami AS, Alkaraiem AA, et al. Multidimensional Health-Related Quality-of-Life Among Patients with Pulmonary Tuberculosis in Saudi Arabia. World Journal of Public Health. 2018;3(2):48–56.
14. Jaber AAS, Ibrahim B. Health-related quality of life of patients with multidrug-resistant tuberculosis in Yemen: prospective study. Health Qual Life Outcomes. 2019;17(1):142.
15. Koethe JR, von Reyn CF. Protein-calorie malnutrition, macronutrient supplements, and tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2016;20(7):857–63.
16. Chandrasekaran P, Saravanan N, Bethunaickan R, Tripathy S. Malnutrition: Modulator of Immune Responses in Tuberculosis. Front Immunol. 2017;8:1316.
17. Mahapatra A, Thiruvengadam K, Nair D, Padmapriyadarsini C, Thomas B, Pati S, et al. Effectiveness of food supplement on treatment outcomes and quality of life in pulmonary tuberculosis: Phased implementation approach. PLoS One. 2024;19(7):e0305855.
18. Ismail N, Ismail F, Omar S V., Blows L, Gardee Y, Koornhof H, et al. Drug-resistant tuberculosis in Africa:

Current status, gaps and opportunities. Afr J Lab Med. 2018;7(2):781.

19. Bade AB, Mega TA, Negera GZ. Malnutrition is Associated with Delayed Sputum Culture Conversion Among Patients Treated for MDR-TB. Infect Drug Resist. 2021;14:1659–67.
20. Dar SA, Shah NN, Wani ZA, Nazir D. A prospective study on quality of life in patients with pulmonary tuberculosis at a tertiary care hospital in Kashmir, Northern India. Indian Journal of Tuberculosis. 2019;66(1):118–22.
21. Dujaili JA, Sulaiman SAS, Hassali MA, Awaisu A, Blebil AQ, Bredle JM. Health-related quality of life as a predictor of tuberculosis treatment outcomes in Iraq. International Journal of Infectious Diseases. 2015;31:4–8.
22. Sineke T, Evans D, Schnippel K, van Aswegen H, Berhanu R, Musakwa N, et al. The impact of adverse events on health-related quality of life among patients receiving treatment for drug-resistant tuberculosis in Johannesburg, South Africa. Health Qual Life Outcomes. 2019;17(1):94.
23. Atif M, Ahmed W, Iqbal MN, Ahmad N, Ahmad W, Malik I, et al. Frequency and Factors Associated With Adverse Events Among Multi-Drug Resistant Tuberculosis Patients in Pakistan: A Retrospective Study. Front Med (Lausanne). 2022;8:790718.
24. Ahmad N, Javaid A, Sulaiman SAS, Afridi AK, Zainab, Khan AH. Occurrence, Management, and Risk Factors for Adverse Drug Reactions in Multidrug Resistant Tuberculosis Patients. Am J Ther. 2018;25(5):e533–40.
25. Nilamsari WP, Rizqi MF, Regina NO, Wulaningrum PA, Fatmawati U. Adverse drug reaction and its management in tuberculosis patients with multidrug resistance: a retrospective study. J Basic Clin Physiol Pharmacol. 2021;32(4):783–7.
26. Zhang Y, Wu S, Xia Y, Wang N, Zhou L, Wang J, et al. Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis in China: An Ambispective Cohort Study. Medical Science Monitor. 2017;23:2348–56.
27. Massud A, Syed Sulaiman SA, Ahmad N, Shafqat M, Chiau Ming L, Khan AH. Frequency and Management of Adverse Drug Reactions Among Drug-Resistant Tuberculosis Patients: Analysis From a Prospective Study. Front Pharmacol. 2022;13:883483.

Case Report

Respiratory Rehabilitation for A Loss to Follow-Up Pulmonary Tuberculosis Patient with Bilateral Hydropneumothorax: A Case Report

Rezky Ahmad Isdiyanta[1], Siti Chandra Widjanantie[2]

[1]Department of Physical Medicine and Rehabilitation,
National Respiratory Referral Center Persahabatan Hospital, Jakarta
[2]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Indonesia, Jakarta

Corresponding Author:
Siti Chandra Widjanantie | Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Indonesia, Jakarta | sitichandraw@gmail.com

Submitted: April 26th, 2024
Accepted: January 21st, 2025
Published: February 28th, 2025

Respir Sci. 2025; 5(2): 82-91
https://doi.org/10.36497/respirsci.v5i2.147

Abstract

Background: Tuberculosis (TB) is a preventable and treatable disease. However, without treatment, mortality from TB is 50%, whereas with treatment, 85% of people with TB can be cured. Incomplete treatment of pulmonary TB can lead to various complications, one is hydropneumothorax, which is an abnormal picture of air and fluid in the pleural cavity. Complications of this condition can lead to long-term impairment of lung function with varying degrees of severity. Pain and shortness of breath are clinical features that interfere with daily activities and are associated with a decreased quality of life. Pulmonary rehabilitation is a crucial component in managing respiratory diseases, including pneumothorax, which aims to restore respiratory muscle strength, optimize lung expansion, and prevent complications such as atelectasis, pleural adhesions, or chronic respiratory insufficiency.

Case: A 26-year-old woman presented to the emergency department with moderate dyspnea. She was diagnosed with loss to follow-up (LTFU) TB with bilateral hydropneumothorax and malnutrition. She was in the third month of a four-drug anti-TB regimen and had a chest tube with water shield drainage (WSD) placed in both the right and left chest walls. The rehabilitation problems in these patients are dyspnea, pain in the chest tube insertion area, immobilization, and partial dependency.

Discussion: A pulmonary rehabilitation program was initiated during hospitalization and continued in the outpatient rehabilitation clinic, including energy conservation techniques, breathing exercises, relaxation, splinted cough, chest wall mobilization, respiratory muscle stretching, and laser therapy for pain management. Barthel Index (BI) shows improvement from 10 to 45 due to pain reduction. Visual Analog Scale (VAS) 7-8 to 5, allowing the patient to use her right upper extremity for daily activities.

Conclusion: Pulmonary rehabilitation is a cost-effective therapy that can improve symptoms and quality of life in patients with post-TB hydropneumothorax. It also reduces spasms, dyspnea, and pain.

Keywords: activities of daily living, hydropneumothorax, infectious disease, rehabilitation, tuberculosis

INTRODUCTION

Tuberculosis (TB) is a major global health issue, with Indonesia being among the countries most heavily impacted by it. According to the World Health Organization's Global TB Report 2023, Indonesia is classified as a high-burden country for TB. Of particular concern is the fact that TB is the second most fatal infectious disease in Indonesia after COVID-19.[1]

Indonesia has the second-highest TB burden in the world after India. The incidence rate in 2021 is 354 per 100.000 population. However, the patient's compliance with the oral TB drug regimen is still low.[2] In 2015, around 40.2% of TB patients in Indonesia had stopped taking their medication before they were declared cured. The patients who have been prescribed medicine for tuberculosis ceased taking it for two months or more without authorization are described as "Lost to Follow Up" (LTFU).[3]

A considerable 26% of patients discontinue their medication due to an improvement or absence of symptoms. For those who have previously received treatment for TB and are classified as LTFU, "Treatment after LTFU" is required. LTFU is the main cause of TB mortality, household transmission, and the proliferation of drug-resistant strains.[4]

Patients with TB, both treated and untreated, can develop respiratory sequelae due to damage to the airway, lung parenchyma, and pleura. Parenchyma lesions may present as tuberculoma, lung cavitation, scarring, and lung destruction. Airway lesions result in the development of bronchyectasis, tracheobronchial stenosis, and bronchiolithiasis. Both contribute to the development of mixed restrictive and obstructive pulmonary disease commonly found in chronic infection.[5]

Tuberculosis with pleural lesions such as hydropneumothorax is commonly found in Indonesia, but published studies on pulmonary rehabilitation for such cases are still limited. Therefore, we present a case of a 26-year-old female LTFU TB patient with bilateral hydropneumothorax in this report.

CASE

A 26-year-old female patient visited the emergency room with recurring difficulty in breathing. She had been experiencing shortness of breath for four months before being admitted to the hospital, which was accompanied by a persistent cough with white phlegm. At the time of admission, the patient's right chest had been inserted into a chest tube for two weeks. She also reported localized pain with a visual analog scale (VAS) score of 8-9.

The patient had a previous history of pulmonary TB in 2014, but she discontinued the treatment on her own after only one month. Despite not experiencing any further symptoms of cough or dyspnea, the patient reported feeling easily fatigued. However, she could still perform her daily activities and work without issues. In 2022, the patient

experienced a loss of body weight, night sweats, increased fatigue, and diarrhea that lasted for two weeks. The patient was diagnosed with lung tuberculosis bacteriological confirmed from RSUD Cengkareng and was given TB medications. The treatment was also stopped after one month due to nausea.

In September 2023, the patient reported sudden shortness of breath, and upon examination, a left pneumothorax was confirmed and a chest tube was inserted. After discharge, daily activity was limited to bed rest. In October 2023, the patient experienced shortness of breath again. A right pneumothorax was diagnosed and a chest tube was placed in the right chest. Two weeks before the admission, both the left and right chest tubes became detached. The right chest tube was reattached at the previous hospital, while the left one was reattached at Persahabatan Hospital just one day ago.

During a physical examination, the patient's Body Mass Index (BMI) was 13.7 kg/m^2, along with muscle wasting and clubbing fingers. During physical examination, notice the patient's neck posture is forward head the tilting of the cervical vertebrae is 40 degrees forward with a rounded shoulder with spasms of pectoralis major.

On respiratory examination, the patient had a respiratory rate of 36 breaths per minute, and their blood oxygen saturation was 98% with a nasal cannula delivering 4 liters of oxygen per minute. The patient had supraclavicular, suprasternal, and epigastric retractions, left-side asymmetrical chest wall movement, and a chest tube inserted in the right thorax. The chest tube has 4 cm undulation and fluid production on the right hemithorax, and the left thorax has 10 cm undulation, with fluid and bubble production. The vesicular sound on the left chest was reduced, and no rales or wheezing sounds were present.

The patient reported dyspnea, which was rated using the Borg scale (13-2-0), and the single breath count test (SBCT) was 5. The modified Medical Research Council (mMRC) dyspnea scale was rated as 4. Barthel Index (BI) was 10; the patient was fully continent for bowel control, but all other parameters were scored 0.

During the diagnostic workup, the chest X-ray on November 26, 2023, revealed findings consistent with possible pneumonia and a differential diagnosis of pulmonary tuberculosis. The right lung was partially collapsed with a right pneumothorax on the chest tube, while the left lung was almost completely collapsed with a left hydropneumothorax on the chest tube, indicating increased fluid density. The patient was also anemic with a hemoglobin of 9.5 g/dL and hypokalemic with a potassium level of 3.38 mmol/L.

Reinsertion of the left chest tube was performed. The patient's pulmonary rehabilitation has begun since hospitalization and consists of posture correction, breathing retraining exercises using deep breathing techniques 5 times/hour, relaxation breathing exercises, respiratory control with splinting in the chest tube insertion area, thoracic mobility

exercises, stretching of the pectoralis, upper trapezius, and rhomboid muscles, and unsupported sitting mobilization as tolerated. After being discharged, she could continue her exercises at home daily. She was given high-level laser therapy on the chest tube insertion area during control in the outpatient rehabilitation clinic to reduce pain.

In addition, the patient was scheduled for spirometry, mycobacteria detection with Mycobacteria Growth Indicator Tube (MGIT), and left lung decortication.

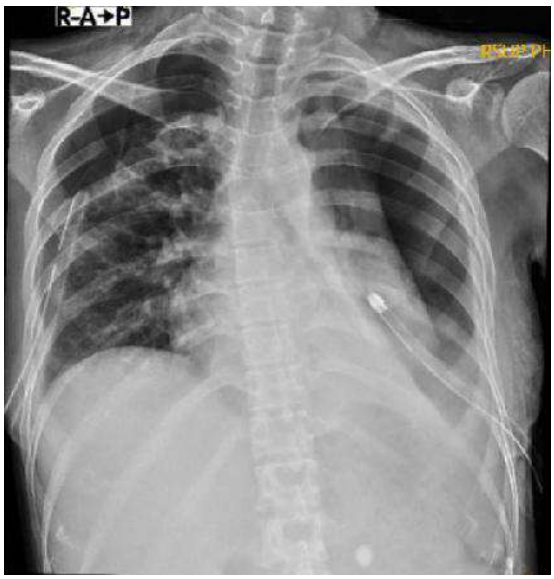


Figure 1. Thoracic x-ray on November 26, 2023

At 1 month of follow-up, the patient was hospitalized again because the left chest tube had detached from the left hemithorax. The tube was subsequently reinserted during a hospital stay. Anemia was found with Hb 8.7 mg/dL, and the patient was given a pack of red cell transfusion.

During observation, the patient appeared short of breath, with a respiratory rate of 20 times per minute, SpO_2 100% with O_2 nasal cannula 6 Lpm, and accessory inspiratory muscle contractions were seen. The patient also experienced pain at chest tube insertion with VAS 7-8.

Figure 2. Robotic High Laser

The rehabilitation program included Transcutaneous Electrical Nerve Stimulation (TENS) and laser therapy in the chest tube area, breathing retraining exercises, chest mobility exercises, respiratory muscle stretching, and energy conservation techniques.

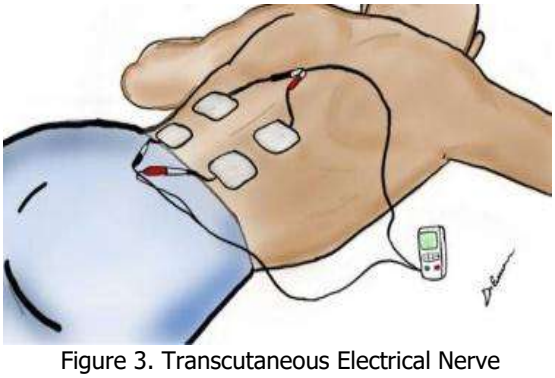


Figure 3. Transcutaneous Electrical Nerve Stimulation (TENS)[6]

Improvement in pain scale to VAS 5 was noted after pain control modalities. Gradual mobilization exercises are carried out to be able to stand upright. During mobilization exercises, the patient is partially assisted to sit on the edge of the bed for 8 minutes; the Borg scale was assessed at 13-3-0. Barthe index showed partial improvement in feeding, grooming, dressing, bladder control, toileting, and transfer, with a final score of 45. Most of the improvement was due to the pain control on the right side of the chest wall, allowing the patient to use her right hand more freely.

At the beginning of the treatment period, the right chest tube was repositioned. After several days of treatment, the left chest tube was removed because no improvement was noted, while the right chest tube was maintained. Spirometry result showed a Vital Capacity of 880 ml (34% of Predicted Vital Capacity), and Forced Expiration Volume at first second (FEV_1)/Forced Vital Capacity (FVC) of 89%, indicating severe respiratory restriction and diffusion problem without obstruction. The patient was scheduled for left lung decortication after the MGIT results showed negative results.

During treatment and exercise, the patient occasionally showed demotivation due to the experience of multiple chest tube detachments. This condition made the patient afraid to move and mobilize. Training with encouragement and supervision made patients more motivated to carry out exercise training during treatment, followed by breathing control and observing vital signs.

The patient was advised to consult the pain division for pain management related to high pain scales. The patient was also advised to consult the psychiatry department to manage demotivating conditions and increase patient adherence to treatment and exercise. Evaluation and management from all related divisions are the key to successfully improving the patient's condition.

DISCUSSION

Pulmonary TB can lead to chronic lung function deterioration.[7] The lung function decreases up to 35% with every infection episode. Post-TB sequelae include non-specific (35%), specific (30%), and obstructive syndrome (33%). About 13% of cases have radiological abnormalities. The patient in this case was diagnosed with pulmonary TB twice but was unable to complete medication due to her intolerance to adverse effects.

Hydropneumothorax is the presence of air and fluid in the pleural cavity, which may occur due to infection or non-infectious causes. Tuberculosis is the most common cause of hydropneumothorax. In TB, the condition usually begins with a focus of infection, which can grow to form a cavity that eventually ruptures, releasing air and fluid into the pleural cavity. An imbalance between the production and absorption of air and fluid in the pleural cavity, and the presence of negative

intrapleural cavity pressure cause damage to continue to occur.[8]

Chest tube insertion is the main management of hydropneumothorax to remove excess air and fluid from the pleural cavity. In a few cases, pleural drainage in more than one hemithorax is required to manage the hydropneumothorax. Survivors of this case are influenced by age, the presence or absence of HIV, and the severity of the lung involved.

The use of a chest tube is usually required for a long duration until the lungs expand, so patients are at risk of experiencing physical inactivity that leads to immobilization, dependence on activities of daily living (ADL), and limited participation. This was seen in the condition of our patient, who had been immobilized for 2 months. This immobilization was worsened as the patient experienced pain with high VAS. Pain intervention plays an important role in the mobilization management of this case. Increased pain tolerance can increase exercise and mobilization adherence.

Most studies of hydropneumothorax patients with chest tubes report shortness of breath as the main clinical symptom. This condition is caused by damage to the pleural wall, causing lung collapse as well as a ventilation-perfusion mismatch. In some cases, the duration of chest tube insertion varied, with an average of 21.3±10.6 days.[9]

Tuberculosis patients showed a longer duration of chest tube requirement (27.1±9.0 days) compared with hydropneumothorax due to other bacteria or malignancies, showing 11.9±3.7 and 10.8±5.3 days, respectively. The average duration of the chest tube insertion was 24.8 days (±13.1) in the study conducted by Kasargod and Awad.[9]

Suta et al in a literature review study, showed that the goal of short-term pulmonary rehabilitation is to reduce dyspnea, anxiety, and depression, while the long-term goal is to maintain the patient's functional status, improve QOL, and facilitate a return to ADL independence.[10]

Pulmonary rehabilitation can be initiated in the acute phase. The goal of the program is to maintain respiratory function and prevent complications such as deconditioning and contractures, using positioning, breathing exercises, active and passive movements and early mobilization. In the acute phase or exacerbation of a chronic condition, it is necessary to assess whether the patient's condition is safe enough to provide exercise.[11]

We provided a pain control management program to facilitate comfortable mobilization for the patient. We started mobilization exercises at a very light level, from sitting upright to sitting on the edge of the bed (Borg scale score between 9-11), with the target up to standing.

Though relatively young and had no history of HIV infection, the severity of the lung damage is extensive, which may delay recovery. Patients with extensive lung disease like this have limited exercise capacity due to impaired gas exchange and

alveolar ventilation. The decrease in oxygen supply to skeletal muscles results in a shift to anaerobic metabolism for energy production.[12] This leads to muscle wasting and fatigue, while extended hospitalization results in muscle deconditioning, depression, and declining quality of life.

Research on pulmonary rehabilitation in TB loss to follow-up patients is limited. However, available studies have demonstrated significant improvements in symptoms, exercise tolerance, and overall quality of life. In addition, according to a previous study by Pontali et al, there are criteria for participation in pulmonary rehabilitation.[12]

This patient meets the Clinical Standards for PTLD (Post TB Lung Disease) recommendations for pulmonary rehabilitation, which include patients with a history of TB, clinical and radiologic symptoms and signs, impaired lung function, reduced exercise tolerance, and comorbidities such as bronchiectasis, pulmonary hypertension, and a history of hospitalization or at least two exacerbations within 12 months.[13]

The recovery of these patients is a complex process. The goal is to improve symptoms and achieve optimal ADL independence. Pulmonary rehabilitation programs are multidisciplinary collaborations and offer several adjustable components depending on the patient's condition.[14,15]

Adequate patient education regarding disease state, treatment, and prognosis is essential to ensure long-term patient compliance. Education regarding comprehensive rehabilitation programs, the importance of physical activity and exercise to improve the quality of life, and compliance with the rehabilitation program also need to be communicated to patients.[14,15]

Since there are very few publications regarding bilateral hydropneumothorax therapy, there are no best protocols for pulmonary rehabilitation in such cases currently available. In this case report, we provide an individualized pulmonary rehabilitation program tailored to the patient's condition and complications. Previous studies by Taketa et al on pneumothorax after esophagectomy surgery suggest very light-intensity walking exercises to avoid exacerbation of pneumothorax.[16]

The pulmonary rehabilitation strategy, in this case, had several limitations. The first was that the patient's perception of pain was very high. Second, most cases of hydropneumothorax are unilateral, but in this case, bilateral hydropneumothorax was found. Third, our patient's physical function did not immediately recover after chest tube reinsertion. This decrease in physical performance reflected the two-month immobilization since the chest tube was first installed.

Inadequate pain control is a barrier in rehabilitation programs, especially for mobilization. Intercostal space nerve blocks can be added as additional pain management, and we recommend consulting a psychiatry department to maintain the patient's motivation and

overcome depression that may arise due to the chronic illness she is suffering from.[17]

Chest tube insertion in this patient resulted in increased pain and immobilization, resulting in chronic pain and difficulty in overcoming the intercostal neuralgia. Pain management that targets the nerves, bones, or tendons that cause pain provides an analgesic effect while reducing the need for opiate consumption.[18]

After chest tube insertion, lung expansion is expected quickly based on studies in most patients. Patients with a diagnosis of hydropneumothorax that lasts more than 10 days, recurrent, or bilateral, is an indication for surgical intervention.[9]

In this case, we administered a combination of breathing exercises, chest mobility exercises, light mobilization, and respiratory muscle stretching, combined with TENS and High-intensity laser therapy set at analgesic type, 3 W, 20 J/cm^2 to control pain and improve dyspnea. This is in line with the study by Namwaing et al, although the results did not influence the length of time the chest tube was installed.[19]

The patient experienced the pain more tolerably with the deep breathing method accompanied by splinting. For chest expansion exercises, we minimized pain by limiting the movement of the shoulders and upper extremities to a level that was tolerable to the patient.

The functional prognosis of this patient was poor. The patient had difficulty carrying out daily activities and is very limited in pain. If the etiology cannot be eradicated, recurrence can also occur. Malnutrition also limits the patient's capacity for exercise.[19] Eliminating the etiology is important, so MGIT was performed to evaluate the possibility of active TB infection before surgery.

Judging from the extent of the existing lung damage and the patient's poor clinical condition, the rehabilitation target for this patient was more akin to palliative care, where the main goal is to improve the patient's quality of life, eliminate or minimize distressing symptoms and complaints, and maintain psychological and spiritual health.

CONCLUSION

Pulmonary rehabilitation should be initiated as soon as possible for patients experiencing reduced lung function due to TB loss to follow-up. The program should be individualized to the patient's condition to reduce respiratory symptoms, improve the ability to perform ADLs and improve quality of life. Interventions can be targeted to reduce muscular spasms, improve dyspnea, and control pain in Hydropneumothorax patients with active TB. Bilateral pulmonary tissue destruction found in this case will limit the benefit of pulmonary rehabilitation intervention. However, palliative goals can still be pursued to optimize ADLs and remaining respiratory function. Long-term monitoring is necessary after intervention to evaluate the patient's progress in performing ADLs and prevent additional infectious exacerbations.

REFERENCES

1. World Health Organization. Global Tuberculosis Report Factsheet 2023. 2023.
2. Kementerian Kesehatan Republik Indonesia. Strategi Nasional Penanggulangan Tuberkulosis di Indonesia. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
3. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization ; 2014.
4. Jiang Y, Chen J, Ying M, Liu L, Li M, Lu S, et al. Factors associated with loss to follow-up before and after treatment initiation among patients with tuberculosis: A 5-year observation in China. Front Med (Lausanne). 2023;10:1136094.
5. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax. 2000;55(1):32–8.
6. Sharif S, Jazaib Ali MY, Kirazlı Y, Vlok I, Zygourakis C, Zileli M. Acute back pain: The role of medication, physical medicine and rehabilitation: WFNS spine committee recommendations. World Neurosurg X. 2024;23:100273.
7. van Kampen SC, Wanner A, Edwards M, Harries AD, Kirenga BJ, Chakaya J, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. BMJ Glob Health. 2018;3(4):e000745.
8. Singh SK, Yadav P, Jatav B, Tiwari KK. Clinicoradiological Profile of Patients with Hydropneumothorax: A Prospective Study of a Hospital Population in Northern India. Indian Journal of Respiratory Care. 2021;10(1):53–6.
9. Kasargod V, Awad N. Clinical profile, etiology, and management of hydropneumothorax: An Indian experience. Lung India. 2016;33(3):278–80.
10. Suta PDD, Silakarma D. The Effectiveness of Pulmonary Rehabilitation in COVID-19 Patients. Surabaya Physical Medicine and Rehabilitation Journal. 2022;4(2):70–80.
11. Shenoy MA, Paul V. Pulmonary Rehabilitation. Treasure Island (FL): StatPearls Publishing; 2025.
12. Pontali E, Silva DR, Marx FM, Caminero JA, Centis R, D'Ambrosio L, et al. Breathing Back Better! A State of the Art on the Benefits of Functional Evaluation and Rehabilitation of Post-Tuberculosis and Post-COVID Lungs. Arch Bronconeumol. 2022;58(11):754–63.
13. Pontali E, Silva DR, Marx FM, Caminero JA, Centis R, D'Ambrosio L, et al. Breathing Back Better! A State of the Art on the Benefits of Functional Evaluation and Rehabilitation of Post-Tuberculosis and Post-COVID Lungs. Vol. 58, Archivos de Bronconeumologia. Sociedad

Espanola de Neumologia y Cirugia Toracica (SEPAR); 2022. p. 754–63.

14. Metin B, Yıldırım Ş, İntepe YS, Ede H, Yıldırım E, Sipahi M, et al. Comparison of different respiratory exercise methods in patients with chest tubes for spontaneous pneumothorax. The Turkish Journal of Thoracic and Cardiovascular Surgery. 2016;24(4):717–21.
15. Topczewsk K, Korwel A, Stangret A, Goryniak-Mikołajczyk A, Szczęśniak A, Mularczyk A. Respiratory and motor rehabilitation in the patients with chest drainage. Journal of Education, Health and Sport. 2019;9(3):111–4.
16. Taketa T, Uchiyama Y, Kodama N, Koyama T, Domen K. Rehabilitation Management for a Patient with Bilateral Pneumothorax after Surgery for Esophageal Cancer. Prog Rehabil Med. 2022;7:20220017.
17. Chushkin MI, Ots ON. Impaired pulmonary function after treatment for tuberculosis: the end of the disease? Jornal Brasileiro de Pneumologia. 2017;43(1):38–43.
18. Chawake V, Yadav V, Jain M, Lakkadsha T, Bhakaney P. Impact of Short-term Exercise Program on Functional Independence in Patient with Hydropneumothorax: A Case Study. J Pharm Res Int. 2021;33(60B):1490–6.
19. Namwaing P, Chaisuksant S, Sawadpanich R, Anukunananchai T, Timinkul A, Sakaew W, et al. Factors Associated with Duration of Intercostal Chest Drainage in Patients with Primary Spontaneous Pneumothorax and the Role of Pulmonary Rehabilitation. Open Access Emergency Medicine. 2021;13:569–73.

Case Report

Cutaneous Adverse Drug Reaction due to Anti-TB Drug Allergy in TB-HIV Patient: A Case Report

Dewi Behtri Yanifitri[1], Yunita Arliny[1]*, Rahmi Hayati[2]

[1]Infection Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin Hospital, Banda Aceh
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin Hospital, Banda Aceh

Corresponding Author:
Yunita Arliny | Infection Division, Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala, dr. Zainoel Abidin Hospital, Banda Aceh| nita.arliny@usk.ac.id

Submitted: November 23rd, 2024
Accepted: February 19th, 2025
Published: February 28th, 2025

Respir Sci. 2025; 5(2): 92-8
https://doi.org/10.36497/respirsci.v5i2.164

Abstract

Background: In people living with HIV/AIDS (PLHIV), tuberculosis (TB) is the leading cause of death, with a 20 times higher risk of developing active TB compared to people without HIV. PLHIV are also at higher risk of experiencing cutaneous adverse drug reactions (CADR) caused by anti-TB drugs. The delayed therapy of TB caused by CADR might make TB management more difficult.

Case: A 23-year-old male with clinically confirmed pulmonary TB on intensive phase anti-TB therapy experienced erythroderma due to allergies to anti-TB drugs and stage III HIV. In the drug challenge, it was found that the patient showed an allergic reaction in the form of a reddish rash that spread widely on the anterior and posterior thorax and abdomen after consuming rifampicin and pyrazinamide.

Discussion: The patient's treatment was then added with cetirizine and methylprednisolone. The anti-TB drugs will be given for 9 months, with the intensive phase of 2 months, and the continuation phase of 7 months.

Conclusion: There is a very high risk of CADR in TB patients with HIV infection. Monitoring the side effects of anti-TB regularly and identifying immediately which anti-TB drug causes the allergy is significant as the key to managing CADR in TB-HIV patients. Anti-TB drug provocation tests for each drug and a gradual dose increase are carried out if the clinical CADR has disappeared or improved.

Keywords: anti-TB Drugs, CADR, Cutaneous Adverse Drug Reaction, People living with HIV/AIDS (PLHIV), tuberculosis

INTRODUCTION

Tuberculosis (TB), which is caused by *Mycobacterium tuberculosis*, is the most common cause of death in people living with HIV/AIDS (PLHIV). The World Health Organization (WHO) reports that PLHIV has a 20 times higher risk of developing active TB than people without HIV. Cutaneous adverse drug reaction (CADR) is one of the various side effects that can occur in TB with HIV patients, which makes the

management indeed a challenge. CADR manifestations can include maculopapular rash, urticaria, fixed drug eruption, angioedema, erythema multiforme, toxic epidermal necrolysis, Steven Johnson Syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS). This side effect can occur due to anti-TB drugs (ATD) or other drugs taken by TB HIV patients.[1–5]

Several studies report that PLHIV is at a higher risk of experiencing CADR caused by anti-TB drugs compared to the general population. The etiology of CADR is not yet known, however, it is believed to be related to changes in drug metabolism, drug interactions, a Th2 cytokine profile that triggers IgE synthesis to drugs, oxidative stress, and hyperactivation of the immune response.[1,3,4] CADR can make TB management more difficult because it can delay therapy or treatment regimens.[6,7]

CASE

Mr. NS, 23 years old, was referred from Aceh Jaya Hospital with chief complaints of itching on the body and redness since 3 days ago. The patient was not complaining of a cough, and there was no history of an old cough. However, the patient had a history of coughing up blood 1 month ago, but then there were no more complaints, like coughing up blood, shortness of breath, nausea, or chest pain. The patient had a history of fever fluctuating 1 month ago, but the fever has subsided.

The patient also complained of night sweats, decreased appetite, and weight loss of 10 kg in the last 3 months. Other than that, the patient complained of diarrhea for 1 month. The patient was subjected to a sputum GeneXpert examination and an HIV test, the results of which indicated the absence of *M. tuberculosis* and the presence of HIV, respectively.

Consequently, the patient was diagnosed with clinically confirmed TB and HIV stage 3. The patient was administered anti-TB medications. Three days before the admission, the patient complained of itching and red rashes that felt hot all over the body while taking the anti-TB. Defecation and urination were normal.

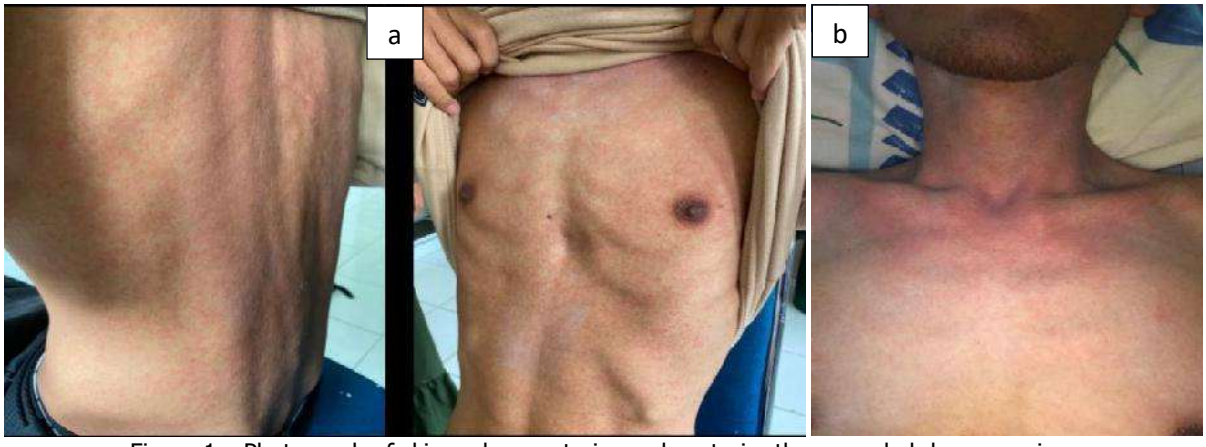


Figure 1a. Photograph of skin rash on anterior and posterior thorax and abdomen region;
1b. on the Colli region after consuming OAT

On the examination, the patient was compos mentis and hemodynamically stable. Physical examination (Figure 1a) revealed a widespread reddish rash on the anterior and posterior thorax and abdomen. Physical examination of the lungs was normal. The X-ray result (Figure 2) also displayed normal lung results.

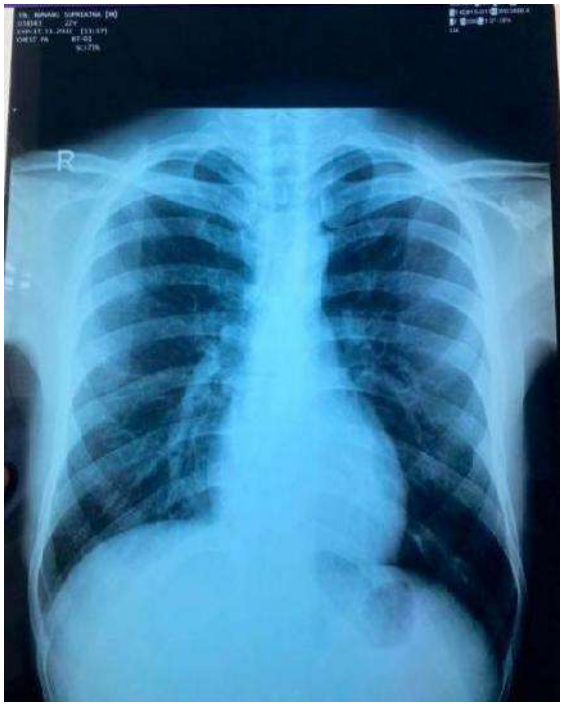


Figure 2. Chest X-ray Results

The working diagnosis of this patient was clinically confirmed pulmonary TB in the first month of the intensive phase, erythroderma et causa allergic to anti-TB drugs, and stage III HIV. A drug challenge was performed on the patient with Isoniazid 1x300 mg, Ethambutol 1x1000 mg, Pyrazinamide 1x1000 mg, and Rifampicin 1x450 mg. During the drug challenge, the patient showed an allergic reaction to Rifampicin and Pyrazinamide. Cetirizine 1x10mg and Methylprednisolone 3x4mg were added to the patient's treatment.

After a drug challenge, we planned to give the anti-TB drugs for 9 months, divided into the intensive phase for 2 months using the regimen 2HEL (Isoniazid, Ethambutol, Levofloxacin), and the continuation phase for 7 months using the regimen of 7HE (Isoniazid and Ethambutol). The patients were also explained about the complications of the disease and the side effects of anti-TB drugs. Periodic evaluation will be carried out on patients with evaluation of clinical, vital signs, laboratory, and drug side effects.

DISCUSSION

Based on the history taking, physical examination, and supporting examinations, the patient exhibited a constellation of symptoms and complaints that led to the suspicion of both TB and HIV. A thorough examination was conducted, encompassing the analysis of sputum for gene Xpert and HIV tests. However, the GeneXpert result showed that the MTB remained undetected, while the HIV test yielded a reactive result. Consequently, the patient was diagnosed with clinically confirmed TB and HIV stage 3. The patient was prescribed a regimen of four fixed-dose combinations (FDC) of anti-TB medications.

After taking the anti-TB drugs, the patient was diagnosed with erythroderma due to an allergy to the anti-TB drugs. In line with the theory from the AAAAI (American Academy of Allergy, Asthma, and Immunology), drug allergies occur due

to drug exposure, which causes an immunological response.[8,9]

In HIV patients, hypersensitivity reactions on the skin are the most common condition (64%). Immune dysfunction in HIV patients causes an increased risk of allergies. In HIV patients, there is an imbalance between T helper (Th) 1 and Th2 cytokines; there is a decrease in Th1 and an increase in Th2 and immunoglobulin (Ig) E. Increased IgE is associated with disease progression. This is thought to be due to viral proteins with allergen-like domains that induce Th2 synthesis. Apart from dysregulation of the immune response, increased CADR in HIV patients is also related to pre-HIV genetic risk, increased oxidative stress, decreased antioxidants, and pharmacological factors, as well as the virus itself.[1–4,10]

Data regarding the incidence of CADR caused by anti-TB drugs in HIV patients is minimal. Widhani et al reported the prevalence of CADR in HIV patients receiving anti-TB drugs is 10.6%, with the most common manifestations of CADR being maculopapular rash (66.7%) and erythema multiforme (14.6%), and only 8.3% experiencing Steven Johnson Syndrome.[1]

In this case, the patient was reported to be allergic to rifampicin and pyrazinamide after 3 days of taking anti-TB drugs. Rifampicin is the most common anti-TB drug reported to cause CADR in HIV TB patients. Widhani et al reported that CADR due to rifampin occurred in 41.7% of TB patients with HIV, followed by ethambutol (16.7%) and pyrazinamide (14.6%). The onset of the emergence of CADR varies from several studies conducted. Generally, it occurs in less than 15 days after starting anti-TB drugs. Tan et al reported that 97% of CADR occurred within 2 months of anti-TB therapy. If CADR occurs after the intensive phase, we need to think about the possibility of other drugs as the cause of CADR.[11,12] Similar results were also reported by Lehloenya et al. Different results were found from research by Tan et al, which mentioned the most common cause of CADR was pyrazinamide, subsequently streptomycin and ethambutol.[13]

This is an important point in considering the order of anti-TB drugs that will be carried out for provocation tests. The anti-TB drugs that are most frequent or most likely to result in CADR should be placed in the last order. The CD4 count should also be an assessment of TB patients with HIV who are at risk for CADR. Severe immunodeficiency conditions, namely a CD4+ count of less than 200 cells/mm^3, can be considered a higher possibility of increasing drug reactions.

The management of patients with anti-TB allergies is divided into two groups: with or without rash.[14] It is recommended for symptomatic treatment to use antihistamines like cetirizine 5-10 mg or diphenhydramine 25-50 mg in patients without rash who complain of itching with no other cause before anti-TB drugs and adding the skin moisturizers for patients with dry skin. If there is no improvement with antihistamines, corticosteroid ointment or oral steroids, such as

prednisolone (10-20 mg daily), can be given. Anti-TB drugs can be continued under close supervision. Side effects usually fade within a few weeks.[15]

In cases of anti-TB allergies with manifestations in the form of skin rashes, the patient must be immediately referred to a referral health facility, and all anti-TB drugs must be stopped immediately. Give intravenous fluids shortly if there is a severe skin reaction involving the mucosa, hypotension, or shock manifestations.[16]

A drug challenge at the referral health facilities can be done to determine the anti-TB drug that may cause the allergic reaction. This helps in determining further management, considering the need for complete treatment in TB patients. After the allergic reaction is under control, the anti-TB drugs are given back gradually, starting with drugs that tend to cause reactions at low doses (H or R), for example, isoniazid 50 mg. The dose is increased slowly over 3 days. We will add one more type of anti-TB the next day if there is no response. Reaction after administering certain anti-TB drugs indicates which drug is causing the allergy. If the anti-TB drug causing the allergy is known, TB treatment can be continued by adjusting the anti-TB drugs.[17]

Anti-TB drugs that cause allergic reactions from the lowest possible risk are Isoniazid, Rifampicin, Pyrazinamide, Ethionamide, Cycloserine, Ethambutol, Para-aminosalicylic acid (PAS), and Streptomycin, with the highest risk. Desensitization can be done sequentially.[18–20]

After the drug challenge was carried out, the patient was found to be allergic to rifampicin and pyrazinamide. The choice of anti-TB regimen for patients with allergic reactions accompanied by rashes is similar to cases of liver disorder due to anti-TB. If the patient is allergic to rifampicin, a regimen with two months of isoniazid, ethambutol, and pyrazinamide without rifampicin is recommended, followed by a continuation phase for 10 months of isoniazid and ethambutol.[17]

If pyrazinamide is discontinued due to an allergic reaction before the intensive phase is completed, the total course of isoniazid and rifampicin is lengthened to 9 months. If there is an allergy to isoniazid and this drug cannot be used, the regimen that can be given is rifampicin, ethambutol, and pyrazinamide for 6-9 months. Lastly, if isoniazid and rifampicin cannot be given simultaneously, streptomycin, ethambutol, and fluoroquinolones can be an option and given for 18-24 months.[17]

The limitation of this study was that the patient was not compared photographically during and after the drug challenge, which shows how the drug challenge affects the skin rash.

CONCLUSION

Tuberculosis patients accompanied by HIV infection are at very high risk of developing CADR. Clinical manifestations of CADR can range from mild to severe, which carries a risk of death. Immune dysregulation is a factor causing CADR in TB patients with HIV. Stopping anti-TB

drugs as soon as possible and identifying the culprit are the keys to managing CADR in TB-HIV patients. It should also be accompanied by the administration of antihistamines and corticosteroids. Anti-TB drug provocation tests for each drug and a gradual dose increase are carried out if the clinical CADR has disappeared or improved.

REFERENCES

1. Widhani A, Karjadi TH, Yunihastuti E, Salwani D, Pramudita A. Cutaneous Adverse Drug Reaction Among HIV-Infected Patients Starting Antituberculosis Treatment. Jurnal Penyakit Dalam Indonesia. 2022 Dec 31;9(4):194–200.
2. Hoosen K, Mosam A, Dlova NC, Grayson W. An Update on Adverse Cutaneous Drug Reactions in HIV/AIDS. Dermatopathology. 2019;6(2):111–25.
3. Oktavriana T, Febrianto B, Hanif I, Arrosyid A, Kamilah L, Heryadi FF, et al. Maculopapular drug eruption in a patient with human immunodeficiency virus (HIV) infection, wasting syndrome and pulmonary tuberculosis: A case report. Jurnal Kedokteran dan Kesehatan Indonesia. 2023;14(3):357–64.
4. Nugroho NP, Kusmiati T. Allergic Reaction due to Anti-Tuberculosis Drugs, How to Manage? Jurnal Respirasi. 2021;7(2):79–85.
5. Jung HY, Park S, Shin B, Lee JH, Lee SJ, Lee MK, et al. Prevalence and Clinical Features of Drug Reactions With Eosinophilia and Systemic Symptoms Syndrome Caused by Antituberculosis Drugs: A Retrospective Cohort Study. Allergy Asthma Immunol Res. 2019;11(1):90–103.
6. Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21: Effectiveness, Toxicity, and Acceptability. Ann Intern Med. 1990;112(6):397–406.
7. Kwon YS, Kim YH, Song JU, Jeon K, Song J, Ryu YJ, et al. Risk Factors for Death during Pulmonary Tuberculosis Treatment in Korea: A Multicenter Retrospective Cohort Study. J Korean Med Sci. 2014;29(9):1226–31.
8. Hamm RL. Drug Allergy: Delayed Cutaneous Hypersensitivity Reactions to Drugs. EMJ Allergy & Immunology. 2016;92–101.
9. Joint Task Force on Practice Parameters, American Academy of Allergy - Asthma and Immunology, American College of Allergy - Asthma and Immunology, Joint Council of Allergy - Asthma and Immunology. Drug Allergy: An Updated Practice Parameter. Annals of Allergy, Asthma & Immunology. 2010;105(4):259-273.e78.
10. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy. 2014;69(4):420–37.
11. Tan WC, Ong CK, Kang SC Lo, Razak MA. Two years review of cutaneous adverse drug reaction from first line

anti-tuberculous drugs. Med J Malaysia. 2007;62(2):143–6.
12. Guo J, Liu ZD, Feng YP, Luo SR, Jiang QM. Assessment of Effective Anti-TB Regimens and Adverse Outcomes Related Risk Factors in the Elderly and Senile-Aged TB Patients. Infect Drug Resist. 2023;16:3903–15.
13. Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. The International Journal of Tuberculosis and Lung Disease. 2011;15(12):1649–57.
14. Caminero JA, García-Basteiro AL, Rendon A, Piubello A, Pontali E, Migliori GB. The future of drug-resistant tuberculosis treatment: learning from the past and the 2019 World Health Organization consolidated guidelines. European Respiratory Journal. 2019;54(4):1901272.
15. Piubello A, Aït-Khaled N, Caminero J, Chiang CY, Dlodlo R, Fujiwara P, et al. Field Guide for the Management of Drug-Resistant Tuberculosis. France: International Union Against Tuberculosis and Lung Disease; 2018.
16. Wilkinson RJ. TB/HIV: A clinical manual. Trans R Soc Trop Med Hyg. 1997;91(4):493.
17. Diel R. Therapie der Tuberkulose. Pneumologe (Berl). 2019;16(2):117–30.
18. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recommendations and Reports. 2020;69(1):1–11.
19. Siripassorn K, Ruxrungtham K, Manosuthi W. Successful drug desensitization in patients with delayed-type allergic reactions to anti-tuberculosis drugs. International Journal of Infectious Diseases. 2018;68:61–8.
20. Mohan A, Sharma SK. Side Effects of Antituberculosis Drugs. Am J Respir Crit Care Med. 2004;169(7):882–3.

Literature Review

The Impact of Klotho Gene Polymorphisms on Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review

Derallah A Lindra[1]*, Endang Purwaningsih[1], Ahmad Rusdan H Utomo[1], Faisal Yunus[2], Makrup E Harahap[3]

[1]Biomedical Science Doctoral Program, University of Yarsi, Jakarta
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta
[3]Raden Mattaher General Hospital, Jambi

Corresponding Author:
Derallah A Lindra | Biomedical Science Doctoral Program, University of Yarsi, Jakarta | ansusadera@yahoo.co.id

Submitted: November 27th, 2024
Accepted: February 19th, 2025
Published: February 28th, 2025

Respir Sci. 2025; 5(2): 99-114
https://doi.org/10.36497/respirsci.v5i2.165

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is linked to persistent inflammation, repetitive strain, and the accelerated aging of the lungs. The Klotho gene is an anti-aging protein that protects cells from inflammation and alveolar damage in COPD patients. At least 10 mutations in the Klotho gene and single nucleotide polymorphisms (SNPs) have been identified in humans. However, the influence of these polymorphisms is not fully understood in COPD patients. This article aims to determine the influence of Klotho gene polymorphisms on COPD patients.

Method: This study employs a systematic review by analyzing secondary data from scientific research articles. Data search using the Google Scholar database. Done using the terms: Polymorphism, COPD, and Alpha Klotho gene.

Results: Four studies were selected for systematic review. Three studies indicate that Klotho gene polymorphisms can cause alveolar destruction, accelerating emphysema occurrence. There is a relationship between Klotho gene polymorphisms and BMI but not with disease severity parameters.

Conclusion: This review indicates that Klotho gene polymorphisms may accelerate emphysema development in COPD patients. There is a relationship between klotho gene polymorphisms and BMI but not with disease severity parameters.

Keywords: Alpha Klotho gene, COPD, polymorphism

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and preventable disease characterized by chronic and persistent airway obstruction. The cause of airway obstruction in this disease is a combination of inflammation of the small airways and lung parenchymal damage. COPD results from the interaction between harmful environmental exposures and genetic predispositions. Smoking is the main environmental factor that can cause COPD.[1,2]

Exposure to other factors, such as smoke from burning biomass and pollution, can cause COPD. Cigarette smoke caused

chronic inflammation and an imbalance in protease-antiprotease activity, causing lung parenchymal damage. Continued lung parenchymal damage will cause remodeling and fibrosis of the lung tissue. However, only about 20% of individuals exposed to these factors develop COPD, suggesting a significant role of genetic susceptibility. This figure shows that environmental factors are not the only factors that play a role.[1,2]

Genetic factors also have a significant influence on the development of this disease. One of them is the occurrence of genetic polymorphism in the development and progression of COPD. Genetic polymorphism refers to the occurrence of two or more alleles at a particular locus in more than 1% of the population.[1,2]

The Klotho gene was discovered in 1997, when studies showed that expression of the protein in mice caused conditions like aging in humans, such as short stature, arteriosclerosis, and osteoporosis. The secreted protein product or transmembrane protein is expressed primarily in the distal renal tubule, choroid plexus, and pituitary gland. However, its effectiveness in humans is unknown. The secreted form inhibits oxidative stress and signaling factors, including insulin/IGF-1, all of which are associated with longevity.[3,4]

Klotho is an important gene located on chromosome 13 and consists of 5 exons. It is a transmembrane glycoprotein with a molecular weight of 135 kDa. Klotho gene expression is thought to predominantly occur in the kidney and brain. It has also been reported in the reproductive and endocrine systems.[5–7]

Klotho is an anti-aging protein that plays an important role in longevity. It plays an important role in preventing various types of cancer, regulating calcium and phosphorus homeostasis, regulating kidney function, and modulating cellular responses. Some preliminary studies have also suggested a link between Klotho and COPD. People with COPD experience decreased Klotho compared to normal people.[5–7]

Several Klotho mutations and single nucleotide polymorphisms (SNPs) have been identified in humans. However, the impact of each SNP is not fully understood. Human studies have investigated the relationship between aging, longevity, and similar traits. The C1818T polymorphism is in exon 4 and is associated with cardiovascular disease, bone density, coronary heart disease, fasting blood sugar, lipid levels, and blood pressure, all of which are prognostic markers. The G395A polymorphism is a mutation in the Klotho region. This polymorphism is associated with blood diseases, high blood pressure, and glucose metabolism.[8,9]

In addition, several studies have also mentioned that the Klotho gene promoter polymorphism G395A is associated with age-related risk factors for various diseases, including muscle wasting, skin wasting, osteoporosis, vascular disorders, calcium deficiency, and emphysema.[10,11] Electrophoretic analysis showed that G-A substitutions in the promoter region affect DNA-protein interactions. Homozygous

mutant mice have defects in Klotho expression and show a syndrome like human aging.[12]

There is still limited research on the influence of Klotho gene polymorphism on COPD. This study aims to investigate the influence of Klotho gene polymorphisms on the development and progression of COPD.

METHOD

This study used a systematic review to map existing literature and identify research gaps. The framework used as a reference in preparing systematic reviews uses PRISMA for systematic reviews, which is a method for increasing quality assurance of the completeness of the systematic review structure and process.

The PRISMA framework was chosen to enhance the quality and completeness of the systematic review. This review follows these steps: 1) identification of relevant articles; 2) screening of articles by title and abstract; 3) full-text eligibility assessment; 4) critical appraisal; and 5) combine data, summarize, and present results.

In this systematic review, the article search uses the PICO (Population, Intervention, Comparison and Outcomes) framework. This framework assists in identifying relevant populations, interventions, comparisons, and outcomes related to Klotho gene polymorphisms and COPD. The description for the PICO framework is as follows:

Table 1. Framework PICO

Framework	Information
Patient/Population/ Problem	Chronic Obstructive Pulmonary Disease
Intervention/ Prognostic factor/ Exposure	The Influence of Klotho Gene Polymorphism on Chronic Obstructive Pulmonary Disease
Comparison/Control	-
Outcome	Klotho Gene Polymorphism on Chronic Obstructive Pulmonary Disease

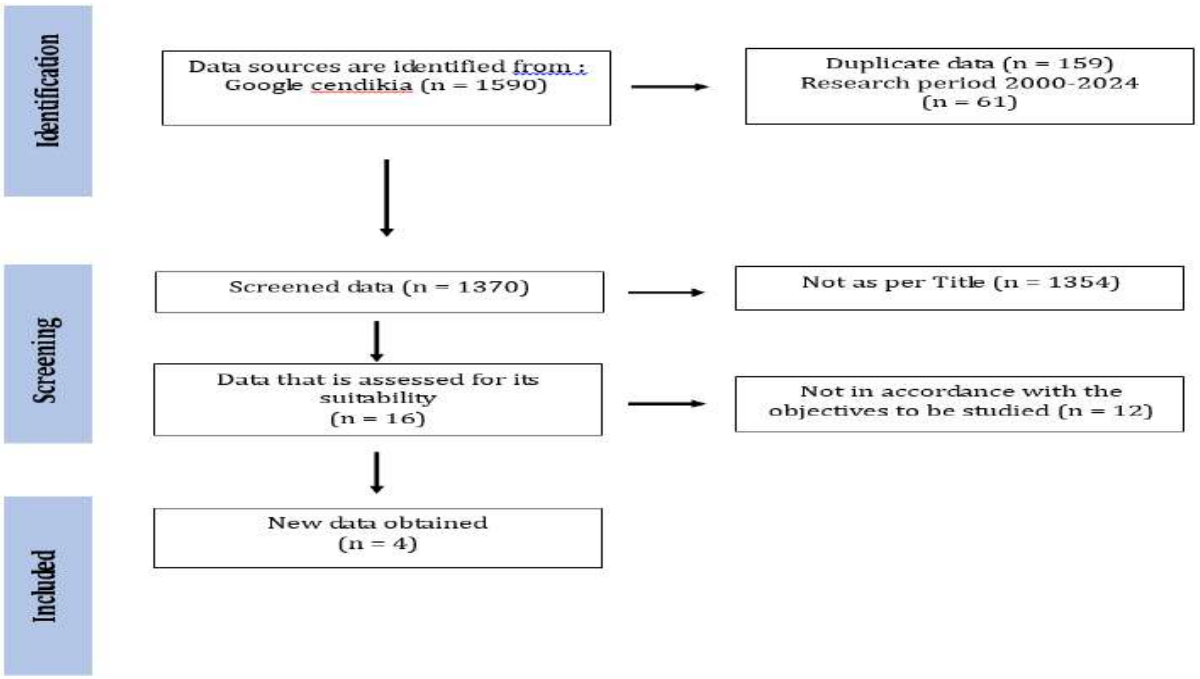


Figure 1. PRISMA for systematic review

The eligibility criteria for articles are specified using inclusion and exclusion criteria. The inclusion criteria used are original articles, published in English, discussing the effect of Klotho gene polymorphism on chronic obstructive pulmonary disease, journals published in 2000-2024, and free full text. The exclusion criteria are review/comment articles, opinion articles, report documents/draft policies/guidelines from WHO/certain formal organizations/thesis reports. Article searches use the Google Scholar database. This review uses the keywords (Polymorphism) AND (COPD) AND (Alpha Klotho Gene).

At the article selection stage, the articles obtained are then screened based on the number of duplicates and the suitability of the article related to the research objectives by paying attention to the title and abstract, analyzing full-text articles according to the inclusion and exclusion criteria.

The search results obtained 4 out of 1590 articles that met the inclusion and exclusion criteria. The search results obtained amounted to 4 studies, then entered a charting data table with the criteria of researchers, research titles, research subjects, methodology, and research results.

Critical appraisal is the process of assessing articles carefully, systematically and relevantly. The author assesses the article using PICO by giving a score of 0=NO, 1=Not Applicable, 2=Unclear, 3=Yes.

The source of data and information for the literature study was obtained from Google Scholar, which collected 1590 literature studies. This literature study consists of articles or journals that have been collected and have been selected based on the title and related abstract information to see whether the article or journal has met the author's inclusion criteria to be used as literature in the literature review, 16 journals were analyzed and 4 selected journals were obtained with the number of literature studies published in 2000, 2010, 2011, 2019, each of which is 1 article or journal.

With the large amount of material that has been collected and reviewed, there is a relationship between the articles or journals obtained, so this literature study can be used as information material and recommendations to determine the polymorphism of the alpha klotho gene in chronic obstructive pulmonary disease (COPD).

RESULT

A total of 1590 articles were identified using the PICO method and specific keywords on Google Scholar. Articles were screened using inclusion and exclusion criteria and assessed for relevance by reviewing titles and abstracts. Four journals were included in this review.

Table 2. Journal Summary

Researcher	Title	Subject	Methodology	Result
Kim WJ, Oh YM, Kim TH, Lee JH, Kim EK, Lee JH, et al[13]	Lack of Association between the Klotho Gene and COPD	• This study included subjects with COPD recruited from "The Korean Obstructive Lung Disease cohort", a prospective longitudinal study of COPD in patients from lung clinics at 11 hospitals in Korea. All COPD subjects in this study had a post-bronchodilator FEV_1/FVC of less than 0.7 and a smoking history of more than 10 packs per year. Complete CT scan data, blood, and other clinical information were obtained from all patients. • In addition, this study also included 305 control subjects consisting of smokers or former smokers with normal lung function who were enrolled in the Korean Genome Epidemiology Study (KoGES)	Data Collection • Data collected included complete CT scans, blood counts, and other clinical information from all patients. • All pulmonary function tests were performed according to the recommendations of the American Thoracic Society/European Respiratory Society. Genotyping • Genomic DNA was isolated from the blood of all patients and SNPs (rs1207568 and rs564481) were genotyped using the TaqMan method with an ABI Prism 7300. Statistical Analysis • The association between COPD susceptibility and SNP genotypes was tested using logistic regression, with adjustment for age, sex, and pack-years of smoking, assuming an additive genetic model. • The association between emphysema severity and SNP genotypes was tested using linear regression after adjustment for age, sex, and pack-years of smoking, assuming an additive genetic model. Data Analysis • All statistical analyses were performed using SAS software (SAS Institute, Cary, NC).	• No association was found between klotho gene polymorphisms and COPD susceptibility in subjects with COPD and controls. • This study has limitations. - First, both COPD groups were predominantly male. The genetic association of the Klotho gene with cardiovascular risk in Koreans was only observed in women, suggesting that the Klotho gene may interact with gender. Given the evidence of gender differences in emphysema, the association of the Klotho gene and emphysema should be studied separately in women. - The second limitation is the relatively small number of subjects. - The third limitation is that we only analyzed two SNPs and we did not genotype the KL-VS variant.

Researcher	Title	Subject	Methodology	Result
Sotiriou I, Kukuvitis A, Chatzikyriakidou A, Tryfon S, Froudarakis ME, Georgiou I, et al[14]	Klotho Gene Polymorphism -395 G>A in Chronic Obstructive Pulmonary Disease (COPD)	Patients included in this study were those who had a confirmed diagnosis of COPD through medical history and pulmonary function tests, had a smoking history of at least 25 packs per year, were of Greek origin, and had no genetic relationship to other patients in the study.	Patient Selection ▪ Patients included in the study had to meet the following criteria: confirmed diagnosis of COPD by medical history and pulmonary function tests, a smoking history of at least 25 pack-years, Greek origin, and no genetic relationship to other patients in the study. ▪ Patients with lung diseases other than COPD, collagen diseases, cancer, metabolic disorders, or non-Greek origin were excluded from the study. Clinical Data Collection ▪ Medical history and tobacco exposure were recorded for each screened patient. ▪ Pulmonary function tests were performed, including measurement of forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and blood gas measurements (PaO_2, $PaCO_2$, pH). ▪ Body mass index (BMI) was calculated by dividing body weight (in kg) by height squared (in m^2). Genetic Analysis ▪ DNA was extracted from peripheral white blood cells using standard salt extraction procedures. ▪ Polymorphism of -395 G>A genotype was screened using the PCR-SSCP (Polymerase Chain Reaction-Single Strand Conformation Polymorphism) method followed by sequence analysis using specific primers. ▪ PCR products were further analyzed by non-denaturing polyacrylamide gel electrophoresis and silver staining to detect SSCP patterns corresponding to each -395 G>A genotype.	• There was a Klotho gene polymorphism (-395 G>A SNP) in COPD patients and it was associated with BMI but not with various parameters of disease severity. • 99 (59.3%) showed the wild-type allele -395 G, 62 (37.1%) were heterozygous (allele –395 G>A), and 6 (3.6%) showed the non-wild-type allele –395 A. • No association of Klotho polymorphism with demographic parameters such as age or gender was observed, although other studies have shown an association of the Klotho gene with advanced age or female gender. • A negative finding of this study is that the COPD patients in this study were all in a small age range and only 5 were female (3%) due to the low incidence of female smokers in Greece

Researcher	Title	Subject	Methodology	Result
			Statistical Analysis ▪ Statistical analysis was performed using StatView 4.5 software. ▪ Mean values were compared between different study groups using unpaired t-tests to reveal significant differences in the distribution of -395 G>A genotypes among COPD patients. ▪ ANOVA test was used to investigate possible associations between clinical data (age, smoking, BMI, FEV_1, FVC, FEV_1/FVC ratio, PO_2, PCO_2, pH) and three -395 G>A genotypes, using mean values and standard deviations. ▪ The chi-square test was used to compare the genotype distributions among the studied parameters.	
Suga T, Kurabayashi M, Sando Y, Ohyama Y, Maeno T, Maeno Y, et al[15]	Disruption of the klotho Gene Causes Pulmonary Emphysema in Mice: Defect in Maintenance of Pulmonary Integrity during Postnatal Life	This study focuses on the analysis of pathological and molecular changes in the lungs of mice with the KL -/- genotype, which is a model for studying emphysema disease. This study includes electron microscopic observation of the lungs, lung function analysis, and Northern blot analysis to assess gene expression related to the pathophysiology of emphysema.	Tissue Preparation and Analysis ▪ Mice were anesthetized with urethane and killed by cutting the abdominal aorta. ▪ Lungs were fixed by intratracheal instillation of 4% paraformaldehyde at a constant pressure of 20 cm H_2O for at least 24 h. ▪ Lung tissues were sliced at 4 μm thickness and stained with hematoxylin and eosin (H&E) for light microscopy. Serial sections were also examined with Kossa staining to detect calcification. Lung Function Analysis ▪ Physiological parameters were measured in mice anesthetized with urethane and breathing spontaneously. Respiratory flow signals were measured via a Lilley-type pneumotachograph connected to an intratracheal tube.	• Emphysema occurs at 4 weeks of age in homozygous klotho mutant mice due to progressive destruction of normal alveolar architecture after normal lung development. Despite impaired respiratory function, the partial pressures of oxygen and carbon dioxide in the arterial blood of homozygous klotho mutant mice are normal, indicating that homozygous klotho mutant mice do not experience respiratory failure at rest. • Ultrastructural analysis of the lungs of KL-/- mice detected calcium deposits on type I collagen fibers in the alveolar septa and degeneration of type II pneumocytes.

Researcher	Title	Subject	Methodology	Result
			▪ Lung volumes were obtained by electrical integration of the flow signals, and intraesophageal pressure was used as the intrathoracic pressure. ▪ Parameters measured included respiratory rate, tidal volume, minute ventilation, expiratory time, dynamic compliance, and total lung resistance. ▪ Northern Blot Analysis ▪ Total RNA was extracted from the lungs of KL -/- mice at 7 to 9 weeks of age, from WT mice at 7 to 9 and 120 weeks of age, and from KL +/- mice at 120 weeks of age. ▪ RNA was separated on a 1% formaldehyde agarose gel, transferred to a nylon membrane, and fixed by ultraviolet exposure. ▪ The membrane was hybridized with a DNA probe labeled with [32P]dCTP using a random primer labeling technique, then washed and exposed to Kodak XR film for autoradiography. Electron Microscopic Observations ▪ Lung specimens were fixed in 3% glutaraldehyde at 4°C and then refixed with 1% osmium tetroxide at room temperature. ▪ Specimens were stained with 1% uranylacetate in 50% ethanol, dehydrated in a graded ethanol series, and finally embedded in agar 100 epoxy resin. ▪ Ultrathin sections (60 nm) were contrasted with lead citrate and examined by electron microscopy.	• Northern blot analysis revealed that the expression of type IV collagen and SP-A was markedly upregulated in homozygous klotho mutant mice at 7 to 9 weeks of age as a compensatory response to the destructive changes in the lung. • Emphysema occurs at 120 weeks of age in heterozygous klotho mutant mice indicating that klotho gene expression is essential for maintaining normal alveolar architecture in adulthood.

Researcher	Title	Subject	Methodology	Result
Sugitani A, Asai K, Watanabe T, Suzumura T, Kojima K, Kubo H, Sato K, et al[16]	A polymorphism rs6726395 in Nrf2 contributes to the development of Emphysema-Associated age in smokers without COPD	• The subjects in this study were 273 healthy individuals who underwent an annual health check-up at MedCity21 Clinic, Osaka City University Hospital, between May and December 2017. All subjects completed a medical interview covering medical history and smoking history (pack-years), physical examination, routine blood studies, pulmonary function tests (PFTs), and high-resolution computed tomography (CT) of the chest. • From the PFT data, 28 subjects were excluded from the study because they had been diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Finally, 245 subjects were enrolled for further analysis.	Definition of Smoker Category ▪ In this study, nonsmokers were defined as participants who smoked less than 10 packs per year, and smokers were defined as participants who smoked more than or equal to 10 packs per year. %LAA Measurement ▪ Chest CT was performed using the Whole Body X-ray CT System [Supria (16ch), Hitachi, Ltd., Tokyo, Japan]. The scan time was 0.75 seconds, and the image matrix was 512 × 512 pixels. Thin-slice CT images with a thickness of 1 mm were reconstructed for all lung fields, and all images were analyzed using Airway Inspector software. ▪ Areas with attenuation less than -950 Hounsfield units were defined as low-attenuation areas (LAA), indicating emphysema, and the ratio of LAA to total area was defined as %LAA. SNP Genotyping ▪ Genomic DNA was extracted from blood samples obtained from each participant using the Gentra Puregene Blood Kit Plus (Qiagen NV, Venlo, The Netherlands). Genotyping of SNP (rs6726395) in Nrf2 gene was performed for each participant with 50 ng genomic DNA, and a pre-designed TaqMan allele-specific polymerase chain reaction (PCR) assay using GeneAmp PCR System (Applied Biosystems, Foster City, CA). Data Analysis ▪ Statistical analysis compared %LAA in clinical variables and each lung area. Data are presented as mean±SD or n (%).	• There is a correlation between Nrf2 gene SNPs and the degree of emphysema-related aging in the Japanese population. • Suggests a gene-environment interaction in the % of upper lung LAA. • The average % of LAA in smokers was significantly higher than that in light non-smokers. • The level of soluble α-klotho, which is identified as an aging suppressor gene, was significantly lower in smokers with COPD. • SNP rs6726395 with the A allele has been reported to have lower Nrf2 expression compared to the G allele [23, 24], and the AG/AA genotype may be susceptible to oxidant-induced lung damage, namely emphysema. • Genotype showed that 52.7% (AA/AG) of the study population were susceptible to smoking-induced emphysema. • CT Scan and Spirometry can only assess current lung conditions, but this study may contribute to the development of COPD prevention concepts.

DISCUSSION

Chuang et al demonstrated an association between circulating α-klotho levels and demographic factors such as ethnicity. The study population had a mean age of 56.1 years, with the majority being White (73.1%), followed by Black (9.1%), Hispanic (11.3%), and other ethnic groups (6.5%). Multiple linear regression analysis showed that women and non-Hispanic Black individuals had higher α-klotho levels compared to non-Hispanic White individuals. Individuals with higher BMI and older ages had lower α-klotho levels.[17]

During follow-up, cox regression analysis suggested that individuals with higher α-klotho levels had a lower mortality risk, with significant differences observed after adjusting for ethnicity. Additionally, multinomial logistic regression analysis showed that individuals with low α-klotho levels were more likely to be current or former smokers, Black, and have a lower BMI and reduced eGFR.[17]

Kim et al found no association between Klotho gene polymorphisms and COPD susceptibility or emphysema severity in COPD patients. Structural changes in lung tissue have been found in aging conditions and pulmonary emphysema. Premature aging reduces patient life expectancy, and atherosclerosis, osteoporosis, and alveolar wall expansion and damage have been associated with Klotho genes. However, the relationship and impact between Klotho genes and alveolar damage are still unclear.[18]

The Klotho gene has been mapped to chromosome 13q12, and several studies have investigated the relationship between Klotho gene polymorphisms and the aging process. For example, the KL-VS allele of the Klotho gene, which contains functional variants, has been found in Czechs, Caucasians, and African Americans and is associated with age-related phenotypes such as coronary heart disease.[18] The Klotho KL-VS allele in the Italian population suggests that the Klotho gene is associated with longevity, but only for a limited period.[19] In contrast, the -395 G>A and C1818T polymorphisms are associated with coronary heart disease, stroke in women, and hypertension.[20–22]

In contrast to the findings in cardiovascular disease, no association was found between SNPs and COPD in the Korean population in the study by Kim et al. The study by Kim et al investigated the association between emphysema severity and Klotho gene polymorphisms in the KOLD cohort study, in which emphysema severity was evaluated using CT.[21]

However, this study failed to find an association and impact between emphysema severity and Klotho gene polymorphisms. This study has several limitations. First, both COPD groups were predominantly male. The genetic association of the Klotho gene with cardiovascular risk in Koreans was only observed in women.[21] Given the evidence for gender differences in emphysema.[23] The second limitation is the relatively small number of subjects. A third limitation is

that we only analyzed two SNPs and did not genotype the KL-VS variant.[13]

The study by Sotiriou et al provides information on the frequency of klotho genotypes in COPD patients and their possible association with age, lung function, GOLD stage, and BMI. No association was found with age, lung function, or GOLD stage, but an association with BMI was observed. This is the first study to report the identification of the Klotho gene in a large group of COPD patients. The heterozygosity for the -395 G>A allele phenotype was 39.1%, which may indicate emphysematous changes of the Klotho gene in the development of lung lesions.[24]

Possible explanations for the shortcomings of this study are that all COPD patients were in a small age range and only 5 were female (3%) and there is a low incidence of female smokers in Greece. None of the disease severity parameters studied, such as GOLD stage, FEV_1, FEV_1/FVC, or blood gases, showed a significant association with the distribution of the klotho -395 G>A genotype. A possible explanation for the lack of association is that most patients in this study had advanced diseases and had very similar lung function parameters. An animal cohort study by Sato et al showed that when emphysema appeared in Klotho mice, their total lung capacity (TLC) was significantly reduced compared with control mice.[24]

Apart from this study, there has been no report on the assessment of klotho gene polymorphism and lung function parameters in patients with COPD. In this study, no association was found between the distribution of Klotho -395 G>A genotypes and smoking habits. In Imamura's study, smoking was shown to be an independent risk factor for coronary heart disease associated with the -395 A allele.[25]

Among the limitations of this study are the lack of confirmation of emphysema by HRCT in the study patients and the absence of a control group. In this study, the Klotho -395 G>A polymorphism was detected in COPD patients. Except for BMI, no other associations were found with clinical parameters, especially those assessing the severity of COPD, including pulmonary function tests, GOLD staging, patient age and smoking history. Given that the Kotho gene is a metabolic gene, the question arises as to whether the mechanism of induction of emphysema by the Klotho deficiency gene in COPD patients is via a possible metabolic pathway.[14]

Research by Suga et al found that the lungs of mice with Klotho homozygous polymorphism (KL-/-) developed normally until the age of 2 weeks. Emphysematous changes first appeared at the age of 4 weeks in KL-/- mice and progressed with age until they died around 8 to 10 weeks. This is a result of progressive damage to normal alveolar architecture after normal lung development.[26]

In addition, Klotho heterozygous polymorphism KL+/- mice that survived more than 120 weeks also showed pulmonary emphysema due to gene

changes in the Klotho gene in lung lesions. These observations indicate that klotho gene expression is essential for maintaining normal alveolar architecture in adulthood.[26]

The respiratory function of KL+/+ mice also matches the respiratory function of patients with pulmonary emphysema. Lung damage in Klotho homozygous polymorphism (KL-/-) mice occurs because the lung ultrastructure of KL-/- mice detects calcium deposits on type I collagen fibers in the alveolar septa and degeneration of type II pneumocytes. The degeneration of type II pneumocytes may impair alveolar cell regeneration in KL-/- mice since type II pneumocytes are known to play an important role in repairing damaged alveoli.[26]

However, northern blot analysis revealed that the expression of type IV collagen and SP-A were markedly upregulated in KL+/+ mice at 7 to 9 weeks of age, when pulmonary emphysema was fully developed. These proteins are thought to exert beneficial effects in preventing emphysematous changes because type IV collagen fibers are an important component of the extracellular matrix and because SP-A has been reported to have a protective function against the development of elastase-induced pulmonary emphysema.[15]

These findings may support the hypothesis of Suga et al that increased expression of the type IV collagen gene is a compensatory genetic response to lung injury. The mitochondrial β-ATPase gene was identified as one of the genes selectively upregulated in the lungs of KL-/- mice by differential screening. Mitochondrial β-ATPase is a subunit of adenosine triphosphate (ATP) synthase, an essential enzyme for ATP synthesis. Northern blot analysis of 13 KL+/+ mice revealed that mitochondrial bATPase expression was increased in most individuals. Mitochondrial β-ATPase plays a critical role in ATP synthesis, and it is likely that decreased expression of this gene ultimately leads to cell death.[15]

The study of Sugitani et al determined that Nrf2 gene polymorphism accelerates the development of aging-related upper pulmonary emphysema in smokers without COPD. Showing a correlation between Nrf2 gene SNPs and the degree of aging-related emphysema in the general Japanese population, and our results suggest a gene-environment interaction in % LAA of the upper lung fields. In several studies of healthy individuals from the general population, Nrf2 SNPs have been shown to correlate with FEV_1.[27]

The hypothesis in the study by Sugitani et al is that Nrf2 SNPs may play a role in the development of aging-related emphysema due to smoking.[28] Cigarette smoke contains a range of harmful substances, including elevated levels of oxidants. Oxidants cause local inflammation, which causes apoptosis in airway epithelial cells and vascular endothelium and causes emphysema. This study found that the average %LAA in smokers was much higher than in nonsmokers.[16]

In this study, the average %LAA in the upper lungs was higher than in the lower lungs, even in smokers without COPD. This study reported that the levels of soluble α-klotho identified as an aging suppressor gene were significantly lower in smokers with COPD. This study focused on the SNP (rs6726395), which has a relatively high minor allele frequency, as the target SNP.[16]

The rs6726395 SNP is in the first intron of the Nrf2 gene. The study found that the %LAA of the upper lung field was significantly correlated with age in smokers with the GG genotype but not in those with the AG/AA genotype. In individuals who are homozygous for the major allele (GG), this reflects the concept that cigarette smoke accelerates the development of aging-related upper lung emphysema, in contrast to the AG/AA genotype with the minor A allele. The A allele of SNP rs6726395 has been shown to result in lower Nrf2 expression compared to the G allele, and the AG/AA genotype may be more prone to oxidant-induced lung damage, such as emphysema.[16]

In this study, genotyping revealed that 52.7% (AA/AG) of the population was susceptible to smoking-induced emphysema. Pulmonary function testing (PFT) is recommended for diagnosing COPD and for early screening of potential or unidentified COPD cases during health check-ups. PFT is a relatively simple and non-invasive method compared to other tests as it does not involve radiation.[16]

In contrast, Nrf2 gene genotyping is less invasive than PFT and CT, requiring only a genomic DNA sample for screening. In addition, genotyping can assess the risk of future emphysema/COPD, whereas PFT and chest CT can only assess the current lungs. Because genotyping can be used to determine susceptibility, genotyping can be a tool that can be used in early prevention efforts.[16]

The results of this study can contribute to the development of this prevention concept. This study population had a limited sample size. Due to this limited sample size, we only identified a small number of smokers with the AA genotype, so this group was combined with the AG genotype group. For this reason, we have not evaluated other SNPs in the Nrf2 gene.[16]

However, in this study, we demonstrated a correlation between SNP (rs6726395) and the degree of aging-related upper pulmonary emphysema in Japanese smokers. This may contribute to personalized treatment or prevention of COPD progression, and Nrf2 may be an intervention target for COPD prevention and treatment.[16]

CONCLUSION

This review suggests that Klotho gene polymorphisms may accelerate emphysema development in COPD patients. Klotho gene polymorphisms were associated with BMI but not with disease severity parameters.

REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
2. García-Sanz MT, Pol-Balado C, Abellás C, Cánive-Gómez JC, Antón-Sanmartin D, González-Barcala FJ. Factors associated with hospital admission in patients reaching the emergency department with COPD exacerbation. Multidiscip Respir Med. 2012;7(1):6.
3. Xu X, Liang X, Hu G, Zhang J, Lei H. Renal Function and Klotho Gene Polymorphisms among Uygur and Kazak Populations in Xinjiang, China. Medical Science Monitor. 2015;21:44–51.
4. Di Bona D, Accardi G, Virruso C, Candore G, Caruso C. Association of Klotho Polymorphisms with Healthy Aging: A Systematic Review and Meta-Analysis. Rejuvenation Res. 2014;17(2):212–6.
5. Zhu Z, Xia W, Cui Y, Zeng F, Li Y, Yang Z, et al. Klotho gene polymorphisms are associated with healthy aging and longevity: Evidence from a meta-analysis. Mech Ageing Dev. 2019;178:33–40.
6. Olejnik A, Franczak A, Krzywonos-Zawadzka A, Kałużna-Oleksy M, Bil-Lula I. The Biological Role of Klotho Protein in the Development of Cardiovascular Diseases. Biomed Res Int. 2018;2018:5171945.
7. Elghoroury EA, Fadel FI, Elshamaa MF, Kandil D, Salah DM, El-Sonbaty MM, et al. Klotho G-395A gene polymorphism: impact on progression of end-stage renal disease and development of cardiovascular complications in children on dialysis. Pediatric Nephrology. 2018;33(6):1019–27.
8. Akbari H, Asadikaram G, Aria H, Fooladi S, Vakili S, Masoumi M. Association of Klotho gene polymorphism with hypertension and coronary artery disease in an Iranian population. BMC Cardiovasc Disord. 2018;18(1):237.
9. Mengel-From J, Soerensen M, Nygaard M, McGue M, Christensen K, Christiansen L. Genetic Variants in *KLOTHO* Associate With Cognitive Function in the Oldest Old Group. J Gerontol A Biol Sci Med Sci. 2016;71(9):1151–9.
10. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature. 1997;390:45–51.
11. Hayashi Y, Okino N, Kakuta Y, Shikanai T, Tani M, Narimatsu H, et al. Klotho-related Protein Is a Novel Cytosolic Neutral β-Glycosylceramidase. Journal of Biological Chemistry. 2007;282(42):30889–900.

12. Kawano KI, Ogata N, Chiano M, Molloy H, Kleyn P, Spector TD, et al. Klotho Gene Polymorphisms Associated With Bone Density of Aged Postmenopausal Women. Journal of Bone and Mineral Research. 2002;17(10):1744–51.
13. Kim WJ, Oh YM, Kim TH, Lee JH, Kim EK, Lee JH, et al. Lack of Association between the Klotho Gene and COPD. Tuberc Respir Dis (Seoul). 2011;71(4):254–8.
14. Sotiriou I, Kukuvitis A, Chatzikyriakidou A, Tryfon S, Froudarakis ME, Georgiou I, et al. Klotho gene polymorphism -395 G<A in patients with chronic obstructive pulmonary disease (COPD). Pneumon. 2010;4(23):348–54.
15. Suga T, Kurabayashi M, Sando Y, Ohyama Y, Maeno T, Maeno Y, et al. Disruption of the klotho Gene Causes Pulmonary Emphysema in Mice. Am J Respir Cell Mol Biol. 2000;22(1):26–33.
16. Sugitani A, Asai K, Watanabe T, Suzumura T, Kojima K, Kubo H, et al. A Polymorphism rs6726395 in Nrf2 Contributes to the Development of Emphysema-Associated Age in Smokers Without COPD. Lung. 2019;197(5):559–64.
17. Chuang MH, Wang HW, Huang YT, Jiang MY. Association between soluble α-klotho and mortality risk in middle-aged and older adults. Front Endocrinol (Lausanne). 2023;14:1246590.
18. Arking DE, Atzmon G, Arking A, Barzilai N, Dietz HC. Association Between a Functional Variant of the KLOTHO Gene and High-Density Lipoprotein Cholesterol, Blood Pressure, Stroke, and Longevity. Circ Res. 2005;96(4):412–8.
19. Invidia L, Salvioli S, Altilia S, Pierini M, Panourgia MP, Monti D, et al. The frequency of Klotho KL-VS polymorphism in a large Italian population, from young subjects to centenarians, suggests the presence of specific time windows for its effect. Biogerontology. 2010;11(1):67–73.
20. Jo SH, Kim SG, Choi YJ, Joo NR, Cho GY, Choi SR, et al. KLOTHO Gene Polymorphism Is Associated With Coronary Artery Stenosis but Not With Coronary Calcification in a Korean Population. Int Heart J. 2009;50(1):23–32.
21. Kim Y, Kim JH, Nam YJ, Kong M, Kim YJ, Yu KH, et al. Klotho is a genetic risk factor for ischemic stroke caused by cardioembolism in Korean females. Neurosci Lett. 2006;407(3):189–94.
22. Rhee EJ, Oh KW, Yun EJ, Jung CH, Lee WY, Kim SW, et al. Relationship between polymorphisms G395A in promoter and C1818T in exon 4 of the KLOTHO gene with glucose metabolism and cardiovascular risk factors in Korean women. J Endocrinol Invest. 2006;29(7):613–8.
23. Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, et al. Sex Differences in Severe

Pulmonary Emphysema. Am J Respir Crit Care Med. 2007;176(3):243–52.

24. Sato A, Hirai T, Imura A, Kita N, Iwano A, Muro S, et al. Morphological mechanism of the development of pulmonary emphysema in klotho mice. Proceedings of the National Academy of Sciences. 2007;104(7):2361–5.
25. Imamura A, Okumura K, Ogawa Y, Murakami R, Torigoe M, Numaguchi Y, et al. Klotho gene polymorphism may be a genetic risk factor for atherosclerotic coronary artery disease but not for vasospastic angina in Japanese. Clinica Chimica Acta. 2006;371(1–2):66–70.
26. Lwebuga-Mukasa JS. Matrix-driven Pneumocyte Differentiation. American Review of Respiratory Disease. 1991;144(2):452–7.
27. Masuko H, Sakamoto T, Kaneko Y, Iijima H, Naito T, Noguchi E, et al. An interaction between Nrf2 polymorphisms and smoking status affects annual decline in FEV1: a longitudinal retrospective cohort study. BMC Med Genet. 2011;12:97.
28. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2013;187(4):347–65.

Literature Review

Diagnosis and Management of Interstitial Lung Abnormalities (ILA): An Article Review

I Wayan Pande Adhyaksa, Fanny Fachrucha*

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta

Corresponding Author:
Fanny Fachrucha | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta | fanny.fachrucha@gmail.com

Submitted: November 4th, 2024
Accepted: February 5th, 2025
Published: February 28th, 2025

Respir Sci. 2025; 5(2): 115-25
https://doi.org/10.36497/respirsci.v5i2.163

Abstract

Interstitial lung abnormalities (ILA) are radiological findings on chest computed tomography (CT) scans that occupy more than 5% of the lung area across upper, middle, and lower lung fields. Interstitial lung abnormalities manifest through several imaging features, including ground-glass opacities (GGO), reticular patterns, diffuse centrilobular nodules, non-emphysematous cysts, honeycombing, and traction bronchiectasis, while emphysema is excluded from its definition. Although global prevalence data for ILA are limited, epidemiological studies report a prevalence ranging from 3% to 10% in various populations. The ILA shares a similar pathological pathway with ILD. Histologically, the structural alterations are caused by a series of inflammations in the parenchyma, the part of the lung that is involved in gas exchange (bronchioles, alveolar ducts, and alveoli). Numerous proteins and pro-fibrotic components reside in this compartment. Connective tissue builds up because of these proteins' recurrent activation cycles. Identified risk factors for developing ILA include advanced age, cigarette smoking, exposure to inhaled substances such as dust and air pollution, and genetic predispositions. The ILA is further categorized into three subtypes: non-subpleural, nonfibrotic subpleural, and fibrotic subpleural, which reflect different radiological characteristics. Currently, there is no definitive treatment for ILA, and management strategies primarily involve clinical assessment, regular radiological follow-ups, and control of risk factors to mitigate disease progression. Given the potential implications of ILA on respiratory health, ongoing research is essential to elucidate its natural history and inform future therapeutic approaches.

Keywords: interstitial lung abnormalities (ILA), prevalence, risk factors, treatment

INTRODUCTION

The identification of pre-clinical interstitial lung disease (ILD) has introduced a term known as Interstitial Lung Abnormalities (ILA), characterized by incidental radiologic findings on computed tomography (CT) scans affecting over 5% of each lung zone. While ILA has emerged as a relatively new concept in imaging diagnostics, its clinical significance remains uncertain. Compounding the issue is the lack of comprehensive global data on the

prevalence of ILA, with estimates from limited epidemiological studies suggesting a prevalence range between 3% and 10% in select populations. This gap in data highlights a pressing need for further research to understand its implications, particularly as ILA may represent the early stages of more severe lung diseases, creating challenges in early detection, management, and patient outcomes.

Both authors did a systematic search of the published literature using Google as the primary search engine to access the Google Scholar and PubMed databases. The search included studies from the inception of these databases up to June 2024 that were written in English. An additional update to the search was carried out in August 2024.

During the screening process, all retrieved titles and abstracts were carefully evaluated by the authors to ensure accuracy and minimize bias. This review emphasized topics of clinical importance to pulmonologists, with a particular focus on the identification, diagnosis, management, and evaluation of patients diagnosed with ILA.

In instances where multiple studies addressed the same topic, the selection process prioritized the most pertinent study, which was determined based on its recency or the significance of its findings in the field. To maintain relevance, the inclusion criteria were restricted to studies published within the last decade.

Consequently, 19 studies were identified and included in this review. Despite employing a systematic and structured approach to the literature search and selection process, the overarching aim of this review was to present a narrative synthesis.

INTERSTITIAL LUNG ABNORMALITIES

Definition

Interstitial Lung Abnormalities are incidental radiologic findings in over 5% of the lung area across upper, middle, and lower zones on thoracic CT scans. Typically found in asymptomatic individuals without prior suspicion of ILD, ILA can potentially progress to more severe forms of ILD, highlighting the need for careful monitoring and risk factor assessment.[1]

Thoracic CT scans in ILA often reveal characteristic features, including ground-glass opacities (GGO) or reticular patterns, indicating early interstitial changes. Common findings also include diffuse centrilobular nodules, non-emphysematous cysts, and more advanced signs like honeycombing, which suggests lung fibrosis, and traction bronchiectasis, where airways are widened due to surrounding fibrosis. These features exclude emphysematous areas, as emphysema involves a distinct alveolar wall destruction process.[2]

If ILA is accompanied by clinical symptoms or impaired lung function, it may indicate the presence of ILD. In such cases, ILA is no longer considered incidental and requires further investigation to confirm or exclude ILD. Additionally, when ILA features are identified during targeted screening for ILD, they are not classified as

ILA, as these findings are expected and not incidental.[3,4]

Epidemiology

The term "ILA" first introduced by Washko et al, has gained recognition in recent years. Although global prevalence data are unavailable, studies report rates between 3% and 10%.[3,5] ILA is more common in individuals aged ≥70, predominantly men (43% vs 26%), and those with a history of smoking.[6]

A multicenter retrospective cohort study in South Korea analyzing thoracic CT scans found ILA in 3% (94 of 2,765) of cases. The prevalence was higher in males (4%; 81 of 2,068) compared to females (2%; 13 of 697) and more common among smokers (4%; 66 of 1,599) than non-smokers (2%; 28 of 1,166).[7]

A cohort study in Canada by Stuart et al found an ILA prevalence of 3.7% (30 of 806 subjects). Among these, 17% had nonsubpleural ILA, 17% had nonfibrotic subpleural ILA, and 67% had fibrotic subpleural ILA. Follow-up thoracic CT scans after two years revealed progressive ILA in 10% of cases, while 90% showed either stability or improvement.[8]

Risk factors

The ILA shares a similar pathological pathway with ILD. Histologically, the structural alterations are caused by a series of inflammations in the parenchyma. Numerous proteins and pro-fibrotic components reside in this compartment. Connective tissue builds up because of these proteins' recurrent activation cycles. Several studies have linked ILA risk to factors such as aging, smoking, inhaled substances, and genetics. The COPDGene study showed an ILA prevalence of 6% in the ≥70 years group, which increases compared to the younger group. Older individuals tend to have higher smoke exposure, though few are active smokers.[9] The risk for developing ILA increases 3.5 times for each 10-year increase in age ($P<0.001$; 95% CI=2.8-4.2), also by 3.6 times increase in mortality ($P<0.001$; 95% CI=3.0-4.5).[10]

Exposure to cigarette smoke is strongly linked to the development of interstitial lung disease (ILD) through fibrosis. In a group of 29,521 people, 9.7% of smokers had ILA, compared to 7.9% of those who never smoked.[11] A study by Sangani et al found that 52.8% of smokers had subclinical ILA or ILD. This group included many with a history of smoking (49%) and an average exposure of at least 30 pack-years.[12] Similarly, Washko et al reported that smokers were 1.82 times more likely to develop ILA. In people who smoked, ILA was associated with smaller lung volumes, reduced exercise ability, and higher death rates.[13,14]

The Multi-Ethnic Study of Atherosclerosis (MESA) found that air pollution is linked to ILA. For every 40 parts per billion (ppb) increase in nitric oxide (NOx), the risk of developing ILA rose by 1.77 times. NOx reacts with other particles in the airways, causing damage through inflammation.[15]

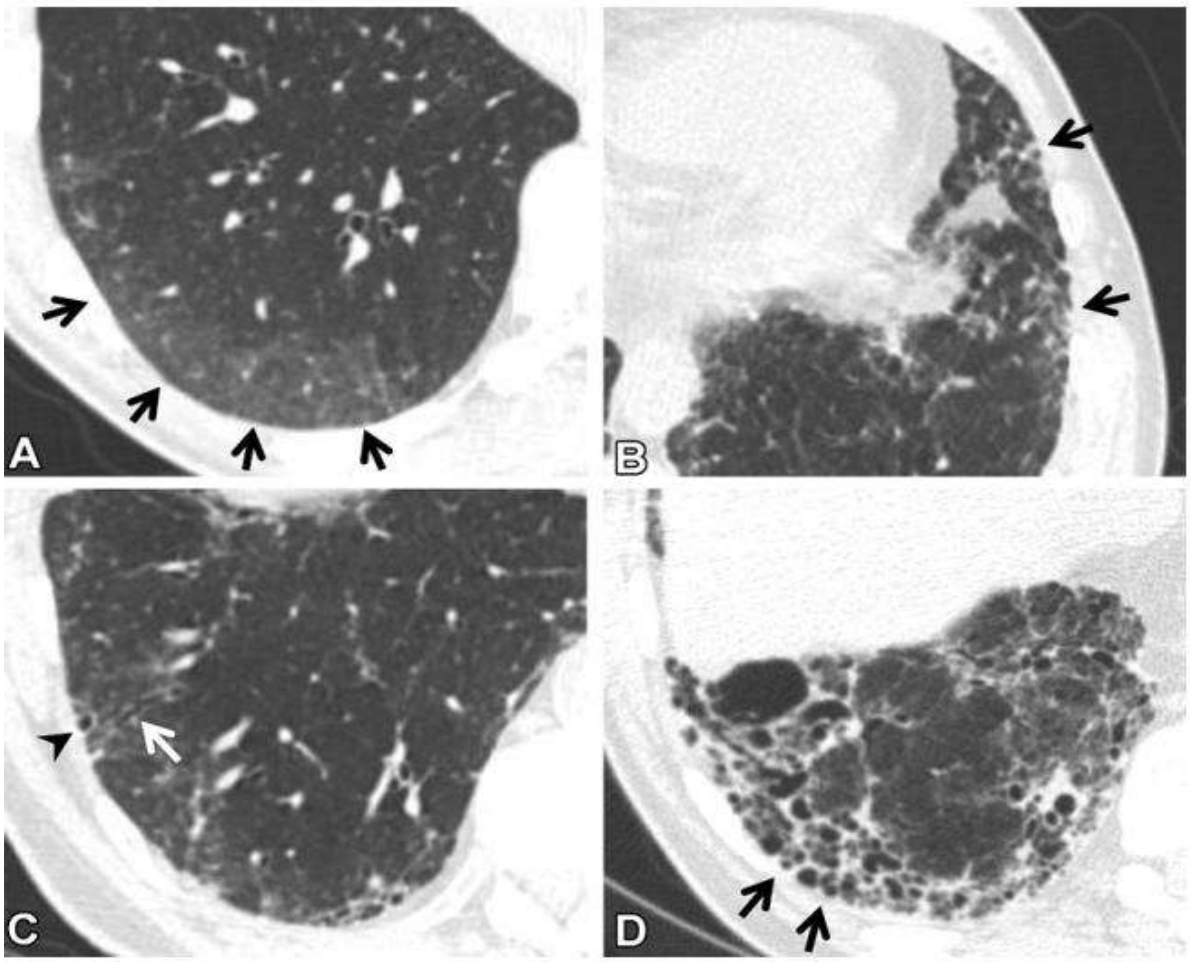


Figure 1. CT scan findings in ILA. Axial slices show ground-glass abnormalities (arrow in A), reticulation (arrow in B), traction bronchiectasis (arrow in C), non-emphysematous cysts (arrowhead in C), and honeycombing (arrow in D)[2]

This process triggers harmful molecules called reactive oxygen species (ROS), leading to ongoing inflammation and the release of chemicals that harm the lungs. Animal studies also showed that NOx exposure can cause lung cell damage, abnormal cell growth, and scarring (fibrosis).[15]

Hata et al discovered a strong link between a genetic variation in the MUC5B gene (rs35705950) and idiopathic pulmonary fibrosis (IPF) as well as familial interstitial pneumonia. This genetic variation was also associated with a higher risk of developing ILA and its progression. People with this variation had a 2.8 times greater risk of ILA compared to those without it.[16] The minor version of this gene occurs in about 10.5% of the population, and having more copies further increases the risk.[9,17] Ivette et al confirmed a strong connection between genetic variations in the MUC5B promoter and ILA. They reported that individuals with these variations were 3.5 times more likely to develop ILA, further supporting the genetic link to the condition.[6]

High levels of certain proteins in the body, like Matrix Metalloproteinase (MMP) 1,7,13, surfactant protein D (SP-D), and resistin, are linked to a higher risk of ILA. However, after considering factors like

age, sex, and lung function, only resistin and MMP-13 were strongly associated with ILA. Some of these proteins, such as MMP-7 and MMP-1, are also thought to be indicators of IPF.[6]

ILA AND IPF RELATION

The ILA and IPF share similarities, particularly their higher prevalence in the elderly, with each decade of age associated with a 2.2-fold increase in ILA risk. Distinguishing between normal aging and progressive ILA is essential to prevent unnecessary monitoring and delays in IPF treatment. Additionally, the male gender is a common risk factor, with male smokers experiencing a 1.7-fold increased incidence of ILA.[1]

Smoking is a well-established independent risk factor for both ILA and IPF. The MESA study linked the severity of parenchymal abnormalities to annual pack consumption.[15] Sack et al found significant associations between air pollution exposure and these conditions, with occupational exposure to pollutants also increasing incidence rates. Specifically, a 40-ppb rise in NOx was correlated with a 1.62-fold increased risk (P=0.06; 95% CI=0.97-2.71) for IPF progression.[1]

The ILA and the IPF differ in definition and characteristics. IPF is marked by a usual interstitial pneumonia (UIP) pattern without a known cause, while ILA is an incidental finding on CT scans. ILA is more common (7% vs. 0.063%) and varies in presentation, unlike the consistently fibrotic and progressive IPF. The histopathology of ILA remains largely unknown.[18]

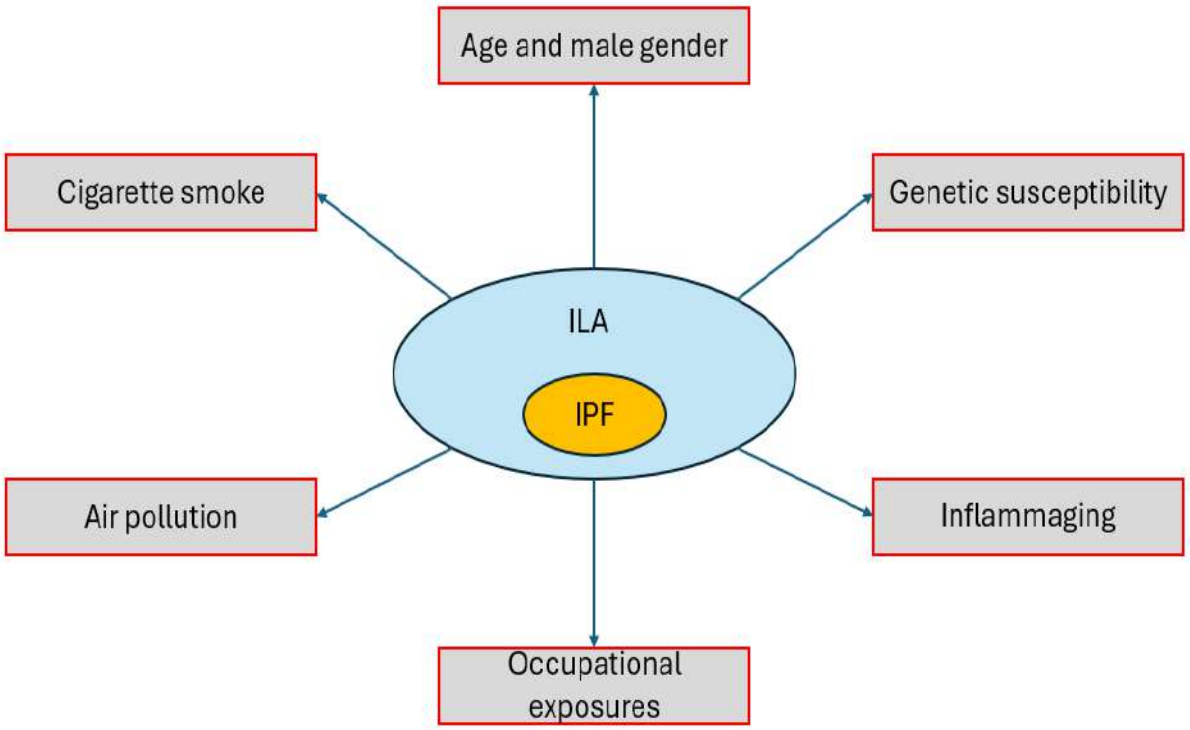


Figure 2. ILA and IPF relation[1]

RADIOLOGICAL FEATURES

The Fleischner Society categorizes ILA into nonsubpleural, nonfibrotic subpleural, and fibrotic subpleural types. The subtypes of ILA are shown in Figure 3. Fibrotic ILA, often with traction or honeycomb bronchiectasis, shows greater progression (P=0.004; OR=6.6) and is associated with higher mortality (P<0.001; HR=1.5). Other studies confirm fibrotic ILA's link to increased mortality risk (P<0.001; HR=1.7).[19]

The prevalence of ILA subcategories differs notably. In a study of 80 subjects, subpleural nonfibrotic ILA was found in 48% of cases, subpleural fibrotic ILA in 30%, and nonsubpleural ILA in 22%. Nonsubpleural ILA was nonprogressive and not linked to increased mortality. In contrast, centrilobular subpleural ILA was associated with greater progression (P=0.004; OR=6.7; 95% CI=1.8-25) and higher mortality risk (aOR=1.6; 95% CI=1.0-2.7; P=0.05). However, centrilobular nodules significantly reduced the likelihood of progression (OR=0.2; 95% CI=0.1-0.5; P=0.002).[1]

Various radiologic features can complicate the diagnosis of ILA by obscuring clinically significant abnormalities. Distinguishing meaningful findings from minor and insignificant ones is essential for identifying cases requiring further evaluation. Although these features are typically not classified as ILA, they can be difficult to differentiate. Comparison with previous images and the use of a pronated CT scan may be necessary for accurate diagnosis.[2]

Centrilobular nodules

Centrilobular nodules, often linked to smoking-related bronchiolitis, are typically non-progressive. Differential diagnoses include infection or aspiration bronchiolitis, hypersensitivity pneumonitis, pneumoconiosis, diffuse alveolar hemorrhage, and lipoid pneumonia.[2]

Apical cap lession

An apical cap is an age-related lesion at the lung apex caused by chronic ischemia, leading to pleural plaque formation or fibrosis. It appears as soft tissue attenuation at one or both apices and is often found incidentally. However, it is not classified as an ILA as it is a distinct radiologic entity.[2]

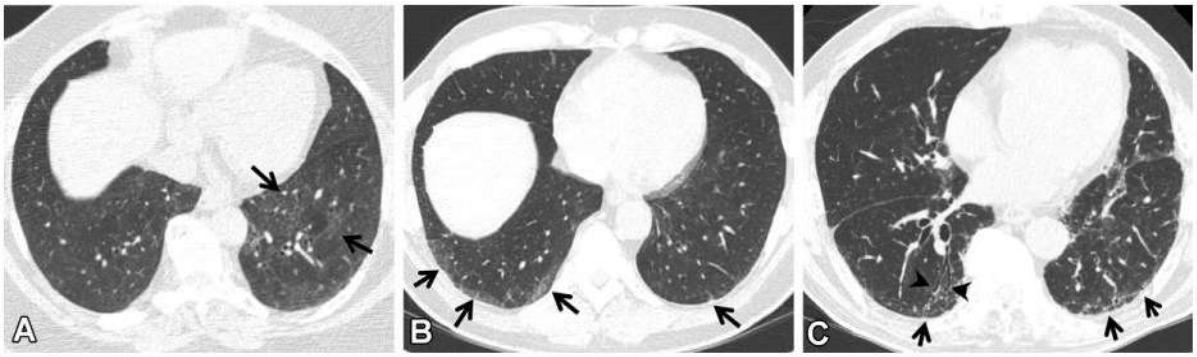


Figure 3. Subcategories of ILA on axial CT images
(A) Nonsubpleural ILA; (B) Nonfibrotic subpleural ILA; (C) Fibrotic subpleural ILA[2]

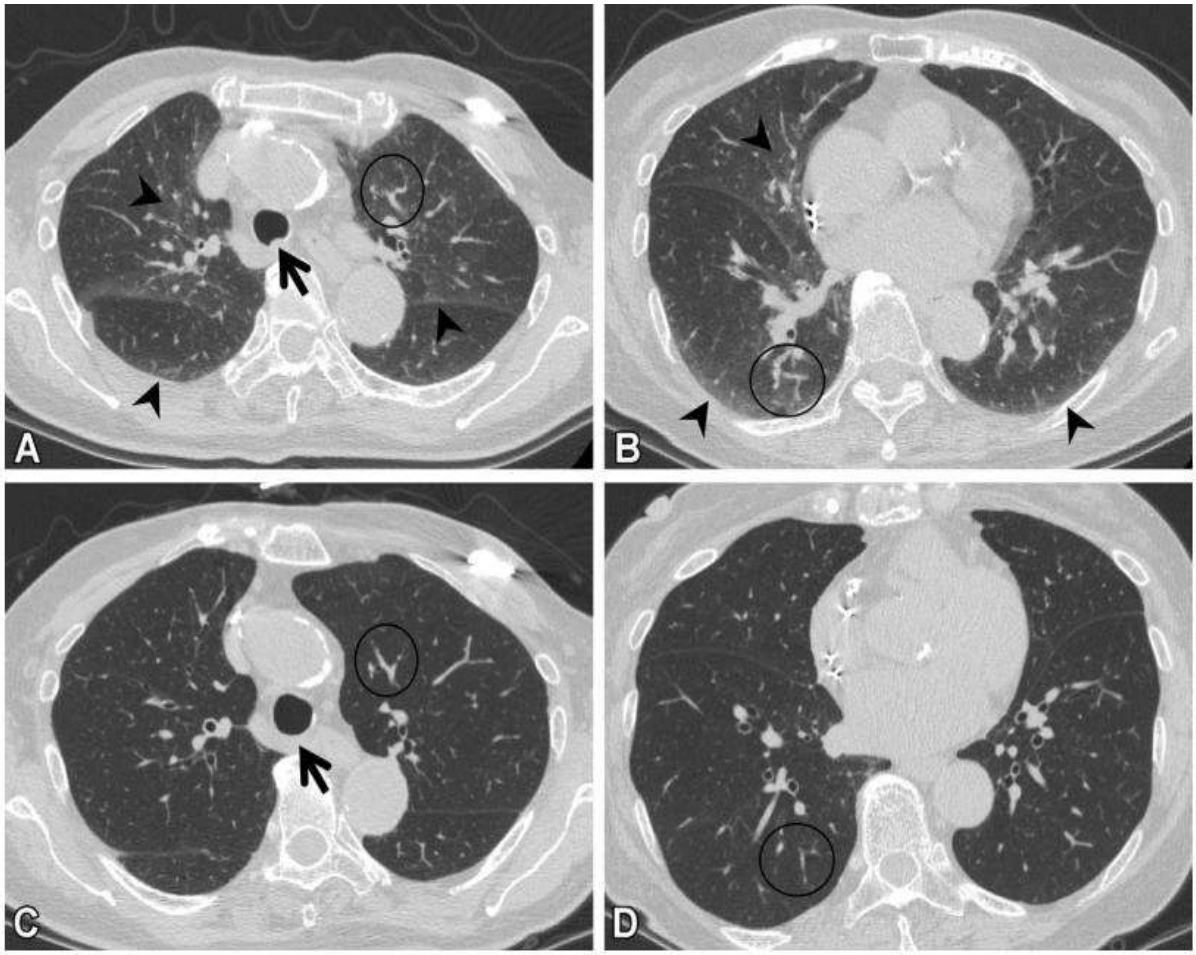


Figure 4. (A, B) CT images show ground-glass abnormalities (arrowheads) in subpleural and central areas of the lung zone. Anterior bulging of the posterior membranous portion of the trachea (arrow in A) and tortuosity of the vessels (circle) suggest a suboptimal inspiration; (C, D) Follow-up axial CT images show that the ground-glass abnormality has disappeared, and the normal round shape of the trachea is seen (arrow in C). The tortuosity of the vessels (circle) is no longer seen[2]

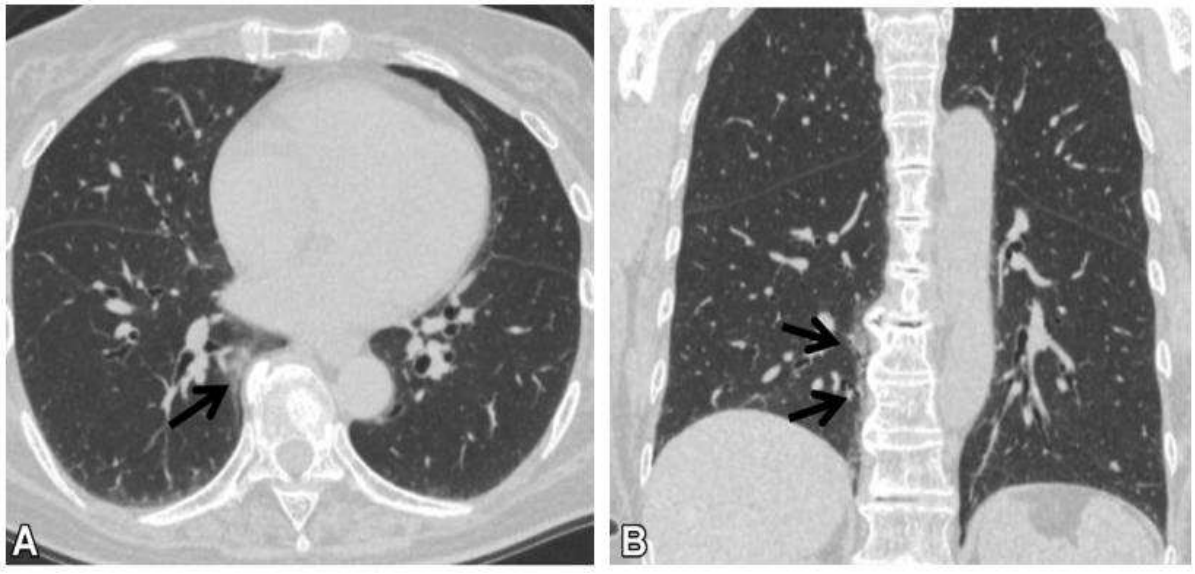


Figure 5. The osteophyte-related lesion in a 72-year-old woman with no respiratory symptoms.
(A) Axial CT image shows ground-glass abnormality adjacent to an osteophyte (arrow)
(B) Coronal CT image shows the craniocaudal alignment (arrows) of the abnormality[2]

Ostheophyte-related lession

Osteophyte-related lesions, including focal reticulation and GGO, are often seen near thoracic vertebral osteophytes on CT scans, particularly in the elderly. These lesions typically appear in the medial right lower lung lobe, as osteophytes are more prominent on the right. These minor abnormalities rarely progress and are not classified as ILA.[2]

Suboptimum inspiration

As we see in Figure 4, GGO abnormalities can result from suboptimal inspiration, where insufficient deep breathing leads to signs like tortuous blood vessels, anterior protrusion of the posterior tracheal membrane, and reduced lung volume compared to prior scans. Distinguishing true ILA often requires both supine and prone CT scans for confirmation.[2]

MANAGEMENT

Currently, insufficient evidence exists to establish a definitive management plan for ILA. The Fleischner Society recommends categorizing individuals as high or low risk based on clinical and radiological factors, following the exclusion of ILD. High-risk individuals present with one or more risk factors. Both groups should aim to reduce risk factors such as smoking and inhalation exposures, and all patients should be educated about the potential long-term effects of ILA.[9]

Low-risk individuals should be re-evaluated if respiratory symptoms or signs of ILD progression, such as reduced lung function, develop. High-risk groups require systematic follow-up. Clinical assessments, including physical exams and pulmonary function tests, are recommended every 3-12 months to monitor ILA progression. Follow-up CT scans should occur every 12-24 months, with earlier scans if symptoms arise. The optimal follow-up interval remains unclear due to limited evidence.[9]

Currently, no specific therapy exists for ILA progression. Antifibrotic agents may reduce progression in fibrotic interstitial lung disease (ILD), with early intervention possibly benefiting high-risk ILA patients. However, the costs and side effects of these treatments necessitate further research to identify higher-risk groups for progression and to understand the natural course of ILA toward clinically significant pulmonary fibrosis.[9]

PROGNOSIS

A 12-year prospective study in Denmark demonstrated increased morbidity in ILA patients, marked by higher rehospitalization rates for respiratory diseases, including chronic obstructive pulmonary disease (COPD), pneumonia, asthma, empyema, and lung cancer. Furthermore, the ILA group had more frequent emergency department visits than the control group. The precise mechanisms underlying this increased morbidity are unclear, but the nonspecific radiologic findings may indicate inflammatory, premalignant, or structural alterations in the pulmonary vasculature.[18]

About 80% of ILA patients showed progressivity on follow-up thoracic CT scans, with fibrotic ILA being a significant risk factor for both ILA progression (HR=10.3; 95% CI=6.4-16.4; P<0.001) and lung cancer (HR=4.4; 95% CI=2.1-9.1; P<0.001). The 10-year mortality rate for patients with fibrotic ILA was 36%, corresponding to a 6.7-fold increased risk of death (HR=6.7; 95% CI=3.7-12.2; P<0.001). Additionally, ILA was associated with a mean decline in forced vital capacity (FVC) of 64 ml per year, 30-35 ml more than normal aging, yet less than the decline seen in IPF patients (±200 ml per year).[1]

Mortality rates among ILA patients vary by study. The Framingham Heart Society (FHS) reported a 7% mortality rate (12 patients) in the ILA group over 4 years, compared to 1% in controls. The Age Gene/Environment Susceptibility (AGES) Reykjavik study found a 56% mortality rate (210 patients) in ILA patients versus 33% (1,065 patients) in non-ILA individuals over 8.9 years. In the COPDGene study, 16% of ILA patients (25 deaths) died compared to 11% (133 deaths) in controls over 6.5 years. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study showed an 11% mortality rate (18 deaths) in the ILA group versus 5% (27 deaths) in non-ILA individuals within 2.9 years.[5]

All the studies, FHS (HR=2.7; 95% CI=1.1-6.5), AGES Reykjavik (HR=1.3; 95% CI=1.2-1.4), COPDGene (HR=1.8; 95% CI=1.1-2.8), and ECLIPSE (HR=1.4; 95% CI=1.1-2.0) showed a substantial increase in mortality risk after controlling for variables. Cardiovascular illness (42%), lung cancer (25%), and respiratory disorders (13%), of which almost half were associated with pulmonary fibrosis, were the main reasons for mortality for ILA patients at AGES Reykjavik.[1,5]

CONCLUSION

In summary, ILA are incidental radiologic findings identified on thoracic CT scans, characterized by more than 5% of lung area involvement. Common imaging features include ground-glass opacities, reticular patterns, diffuse centrilobular nodules, non-emphysematous cysts, honeycombing, and traction bronchiectasis. Risk factors for ILA encompass age, gender, smoking, inhalation exposures, genetic polymorphisms, and elevated inflammatory biomarkers. Assessing ILA can be complicated by overlapping radiologic features, necessitating comparisons with prior imaging and, when appropriate, prone-position scans.

Current management approaches are primarily conservative, focusing on risk stratification, exposure reduction, and follow-up evaluations within 6-12 months. Patients with ILA face increased morbidity from respiratory conditions and heightened mortality risk, highlighting the need for continued research and careful clinical monitoring in this demographic.

Future ILA research faces several difficulties. The Fleischner Society's

recently suggested definition of interstitial lung abnormalities must be widely accepted to compare various ILA studies, not just ILA in general, but also ILA subtypes and imaging patterns. In addition to a recent expert review, clinical studies on the most effective ways to evaluate and monitor individuals with ILA are required. These investigations should focus on biomarkers that may reveal which individuals are at risk, particularly blood-based biomarkers because of their widespread usage in clinical practice and ease of access. It is feasible that the value of ILA biomarker research might not only forecast ILA development and ILD-related mortality but extend to predicting more severe clinical outcomes linked to ILA, such as cancer and death from all causes.

REFERENCES

1. Tomassetti S, Poletti V, Ravaglia C, Sverzellati N, Piciucchi S, Cozzi D, et al. Incidental discovery of interstitial lung disease: diagnostic approach, surveillance and perspectives. European Respiratory Review. 2022;31(164):210206.
2. Hata A, Hino T, Yanagawa M, Nishino M, Hida T, Hunninghake GM, et al. Interstitial Lung Abnormalities at CT: Subtypes, Clinical Significance, and Associations with Lung Cancer. RadioGraphics. 2022;42(7):1925–39.
3. Axelsson GT, Gudmundsson G. Interstitial lung abnormalities – current knowledge and future directions. Eur Clin Respir J. 2021;8(1):1994178.
4. Ledda RE, Milanese G, Milone F, Leo L, Balbi M, Silva M, et al. Interstitial lung abnormalities: new insights between theory and clinical practice. Insights Imaging. 2022;13(1):6.
5. Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. JAMA. 2016;315(7):672–81.
6. Buendía-Roldán I, Fernandez R, Mejía M, Juarez F, Ramirez-Martinez G, Montes E, et al. Risk factors associated with the development of interstitial lung abnormalities. European Respiratory Journal. 2021;58(2):2003005.
7. Lee JE, Chae KJ, Suh YJ, Jeong WG, Lee T, Kim YH, et al. Prevalence and Long-term Outcomes of CT Interstitial Lung Abnormalities in a Health Screening Cohort. Radiology. 2023;306(2):e221172.
8. Stuart K, Ahmad M, Lok SD, Gillson AM, Bédard ELR, Tremblay A, et al. Prevalence and outcomes of interstitial lung abnormalities in a Canadian lung cancer screening trial. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2023;7(3):140–3.
9. Hata A, Schiebler ML, Lynch DA, Hatabu H. Interstitial Lung Abnormalities: State of the Art. Radiology. 2021;301(1):19–34.

10. Sanders JL, Putman RK, Dupuis J, Xu H, Murabito JM, Araki T, et al. The Association of Aging Biomarkers, Interstitial Lung Abnormalities, and Mortality. Am J Respir Crit Care Med. 2021;203(9):1149–57.
11. Patel AS. Interstitial lung abnormalities: do symptoms matter? ERJ Open Res. 2023;9(5):00502–2023.
12. Sangani RG, Deepak V, Ghio AJ, Forte MJ, Zulfikar R, Patel Z, et al. Interstitial lung abnormalities and interstitial lung diseases associated with cigarette smoking in a rural cohort undergoing surgical resection. BMC Pulm Med. 2022;22(1):172.
13. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, et al. Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities. New England Journal of Medicine. 2011;364(10):897–906.
14. Grenier PA. Relationship between Interstitial Lung Abnormalities and Emphysema in Smokers with and Those without COPD. Radiology. 2018;288(2):610–1.
15. Sack C, Vedal S, Sheppard L, Raghu G, Barr RG, Podolanczuk A, et al. Air pollution and subclinical interstitial lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA) air–lung study. European Respiratory Journal. 2017;50(6):1700559.
16. Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, et al. Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study. Am J Respir Crit Care Med. 2016;194(12):1514–22.
17. Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, et al. MUC5B Promoter Polymorphism and Interstitial Lung Abnormalities. New England Journal of Medicine. 2013;368(23):2192–200.
18. Hoyer N, Thomsen LH, Wille MMW, Wilcke T, Dirksen A, Pedersen JH, et al. Increased respiratory morbidity in individuals with interstitial lung abnormalities. BMC Pulm Med. 2020;20(1):67.
19. Putman RK, Gudmundsson G, Axelsson GT, Hida T, Honda O, Araki T, et al. Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019;200(2):175–83.

Literature Review

Exploring Epigenetic Landscapes in COPD: Therapeutic Implications and Recent Insights

Aditya Wirawan[1]*, Tutug Kinasih[1], Rania Imaniar[1], Hario Baskoro[1], Budhi Antariksa[1], Naohisa Matsumoto[2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta
[2]Department of Respiratory Medicine, Juntendo University Faculty of Medicine, Tokyo

Corresponding Author:
Aditya Wirawan | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta | wirawan_aditya84@yahoo.com

Submitted: December 19th, 2024
Accepted: February 10th, 2025
Published: February 28th, 2025

Respir Sci. 2025; 5(2): 126-40
https://doi.org/10.36497/respirsci.v5i2.166

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of global mortality, primarily driven by an abnormal inflammatory response to harmful particles and gases. This review explores the epigenetic mechanisms underlying COPD pathogenesis and their therapeutic implications. A comprehensive literature review was conducted, analyzing recent findings on DNA methylation, histone modifications, and noncoding RNAs (ncRNAs) in COPD. Key studies highlighting the impact of these epigenetic changes on inflammation, cellular responses, and disease progression were evaluated. Our review highlights that epigenetic modifications, such as DNA methylation and histone modifications, significantly impact gene expression without altering the DNA sequence. Cigarette smoking has been shown to influence both DNA methylation and histone acetylation, leading to inflammatory responses and the exacerbation of COPD. These modifications contribute to chronic inflammation and disease progression, with alterations in histone acetylation, methylation, and phosphorylation playing critical roles in COPD pathogenesis. The interplay between epigenetic changes and environmental factors, particularly tobacco smoke, reveals a complex mechanism driving COPD progression. Aberrant gene expression linked to these epigenetic modifications suggests potential disease severity and progression biomarkers. Targeting these alterations offers novel therapeutic strategies. Emerging treatments, such as quercetin and theophylline, promise to restore normal cellular functions and effectively manage COPD. Future research should focus on elucidating these mechanisms further and developing targeted therapies to mitigate the impact of epigenetic modifications on COPD.

Keywords: chronic obstructive pulmonary disease, DNA methylation, epigenetics, histone modifications, therapeutic strategies

INTRODUCTION

COPD, recognized as the third leading cause of mortality globally by 2020, is characterized by mucociliary dysfunction, lung inflammation, airway fibrosis, alveolar destruction, and chronic

bronchitis with mucus hypersecretion.[1–3] Affecting millions worldwide, COPD significantly contributes to both morbidity and mortality, representing a substantial health burden with high associated healthcare costs.[4]

According to the World Health Organization (WHO), the number of COPD cases is projected to increase by 30%, reaching approximately 4.6 million people by 2030.[5] This rising prevalence is primarily driven by continued tobacco use, the major risk factor for COPD, along with indoor air pollution, occupational exposures, and an aging global population. Cigarette smoke, containing over 4,700 chemical compounds and 10^{14} free radicals/oxidants, plays a central role in COPD pathogenesis and its associated inflammatory responses.[6]

COPD is a complex disease influenced by genetic predispositions, environmental exposures, and epigenetic modifications within a developmental context. Recent studies emphasize the critical yet underexplored role of genetic susceptibility, including epigenetic changes, in the development and progression of COPD. Epigenetic mechanisms, such as DNA and RNA methylation, histone modifications, and noncoding RNAs, modulate the response of lung epithelial cells and macrophages to harmful substances, including cigarette smoke and oxidants.[7]

These epigenetic modifications, such as DNA and RNA methylation, histone modifications, and noncoding RNAs, influence gene expression temporally and spatially without altering the underlying DNA sequence.[8] For instance, cigarette smoking induces DNA methylation, which in turn activates inflammatory pathways contributing to COPD pathogenesis.[9]

Despite advancements in understanding COPD, the disease remains incurable. However, symptomatic treatments can help mitigate disease progression and improve patient outcomes. This review aims to provide a comprehensive overview of current evidence regarding epigenetic changes associated with COPD. Furthermore, understanding these epigenetic alterations could pave the way for personalized treatment approaches, potentially reducing the burden of chronic lung diseases.

EPIGENETICS AND PULMONARY DISEASES

Epigenetic regulation of gene expression and protein synthesis involves a range of well-established mechanisms essential for normal development and cellular adaptation to maintain homeostasis. These mechanisms ensure that genetic information is appropriately expressed in response to environmental and physiological changes.[10]

Epigenetics encompasses inheritable chromatin structure and biochemistry alterations that do not involve changes to the DNA sequence itself. These processes affect both normal and disease states by modulating gene expression. The primary epigenetic mechanisms extensively studied include DNA methylation, histone

modifications, and non-coding RNAs (ncRNAs).[11]

Research increasingly highlights the role of epigenetics in developing various pulmonary diseases, such as COPD and asthma. These conditions emerge from complex interactions between environmental factors, such as cigarette smoke and pollution, and genetic susceptibility, leading to altered gene expression without changes in the DNA sequence. Epigenetic modifications regulate crucial processes like inflammation, fibrosis, and airway remodelling in the lungs. For example, exposure to cigarette smoke has been shown to induce changes in histone modification patterns and DNA methylation, contributing to chronic inflammation and oxidative stress.[12]

Reduced histone deacetylases (HDACs) activity in COPD has been associated with intensified inflammatory responses and decreased effectiveness of corticosteroids.[3,13] Research indicates that targeting epigenetic modifications through HDAC inhibitors or DNA methylation modulators could be a promising therapeutic strategy for addressing these abnormal gene expression patterns.[3]

EPIGENETIC MECHANISM OF COPD

COPD is a complex disorder influenced by a combination of genetic factors, environmental exposures, and epigenetic changes within a developmental framework. Investigating the epigenetic basis of COPD can offer an unbiased assessment of key molecular elements involved in its pathobiology, potentially revealing new insights into the mechanisms that drive the disease. COPD is a complex and varied condition within the lung that involves damage to the lung parenchyma, leading to a reduction in elastic recoil (emphysema) and disease affecting the small airways.[14] COPD is characterized by progressive airflow obstruction, which may result from emphysema-related damage to lung tissue, fibrosis and destruction of small airways, and/or excessive mucus production typical of chronic bronchitis.[2]

Smoking is the most significant risk factor for COPD, with research highlighting its impact throughout an individual's life, from prenatal exposure to old age, and showing that smoking induces extensive epigenetic changes that can persist long after cessation.[15] In addition to smoking, exposure to other harmful inhalants, such as biomass combustion products, is also a well-documented risk factor for COPD.[2] The review underscores how epigenetic modifications lead to aberrant gene expression that drives inflammatory and fibrotic processes in COPD.

DNA Methylation

DNA methylation is one of the most extensively studied epigenetic mechanisms due to its crucial role in regulating gene expression. This modification involves the covalent attachment of a methyl group to the 5' carbon of cytosine within cytosine-phosphate-guanine (CpG) dinucleotide sequences in the genome, influencing

gene regulation.[16] DNA methylation is catalyzed by DNA methyltransferases (DNMTs) and is essential for various biological processes, including gene silencing, imprinting, and X-chromosome inactivation. Aberrations in DNA methylation are linked to several diseases, including COPD.[17]

Variations in DNA methylation are linked to COPD status and can impact gene expression for specific genes. The methylation profiles differ between airway and parenchymal fibroblasts, indicating that DNA methylation affects disease pathology differently in these distinct lung tissue types.[14] The reversibility of DNA methylation, influenced by the duration and intensity of smoking exposure, suggests that it could serve as a potential biomarker for COPD.[18]

This altered methylation status reduces the expression and activity of cyclo-oxygenase-2 (COX-2) in pulmonary vascular endothelial cells, potentially contributing to endothelial apoptosis in COPD.[19] Recent research suggests that the apoptosis of structural cells in the lung is a crucial upstream event in COPD pathogenesis.[20]

Studies have demonstrated that genes such as COX-2 undergo hypermethylation, leading to chronic mucus hypersecretion, airway fibrosis, and persistent inflammation in the lungs.[9] This dysregulation exacerbates the inflammatory response and contributes significantly to COPD progression.[21,22] Prostacyclin, another cyclo-oxygenase product, may offer protection against emphysema by slowing apoptosis in the lung's microvascular endothelium.[23]

In COPD, cigarette smoking is a major driver of abnormal DNA methylation. The harmful chemicals in cigarette smoke induce the methylation of genes related to inflammation, oxidative stress, and apoptosis.[20] The epigenetic changes induced by cigarette smoke can persist even after smoking cessation, underscoring the long-term impact of smoking on lung tissue. These alterations affect gene expression and contribute to corticosteroid resistance and chronic airway remodelling, complicating disease management.[16]

Differentially methylated sites (DMSs) can be integrated into current models for predicting COPD risk, offering more accurate predictions than traditional clinical variables alone. DMSs from peripheral blood have both predictive and clinical significance, making blood a promising tissue for biomarker development due to its accessibility and the possibility of repeated sampling.[16] Understanding DNA methylation's role in COPD pathogenesis could lead to potential therapeutic strategies, such as targeting DNMTs or reversing abnormal methylation patterns to alleviate inflammation and slow disease progression.[24]

Armstrong et al identified specific CpG loci with significant methylation differences (such as HSH2D [Hematopoietic SH2 Domain Containing], SNX10 [Sorting Nexin 10], CLIP4 [CAP-Gly domain containing linker protein family member 4], and TYK2 [Tyrosine Kinase

2]), which are linked to genes involved in immune response, inflammation, and metabolism.[1,25]

These epigenetic modifications may contribute to the functional heterogeneity of macrophages, influencing processes such as pathogen defense, inflammatory regulation, and energy metabolism in the lungs.[1,25] Methylation of the chromosome 10 open reading frame 11 (C10orf11) gene, which has been linked to COPD through genome-wide association studies (GWAS), was detected in the airway epithelial cells and lung tissues of smokers who developed COPD.[26]

Cigarette smoking can lead to methylation changes in the promoter region of the mitochondrial transcription factor A (mtTFA) gene. Peng et al discovered that DNA methylation levels of the mtTFA promoter were significantly higher in individuals with COPD, which resulted in reduced mtTFA mRNA expression in the lungs.[27]

In cigarette smoke extract (CSE)-treated human umbilical vein endothelial cells (HUVECs), both mtTFA mRNA and protein expression were similarly downregulated due to hypermethylation of the mtTFA promoter. This cigarette smoke-induced hypermethylation is associated with the initiation and progression of COPD. The study suggests that demethylation agents targeting mtTFA hypermethylation, such as the methylation inhibitor 5-aza-2'-deoxycytidine (AZA), could restore mtTFA expression and potentially offer a novel therapeutic approach for COPD.[27]

The primary risk factor for COPD is inhaling harmful particles, such as cigarette smoke, which damages the airway epithelium and initiates inflammation. In COPD patients, cigarette smoke induces hypomethylation of Aryl Hydrocarbon Receptor Repressor (AHRR) in airway epithelial cells, leading to increased AHRR expression and reduced aryl hydrocarbon receptor (AHR) expression, impairing its protective effects. Increased expression of AHRR in airway epithelial cells could result in disrupted mitochondrial function and apoptosis/necroptosis induced by cigarette smoke, potentially leading to uncontrolled cell death.[28]

The primary risk factor for COPD is inhaling harmful particles, such as cigarette smoke, which damages the airway epithelium and initiates inflammation. In COPD patients, cigarette smoke induces hypomethylation of AHRR in airway epithelial cells, leading to increased AHRR expression and reduced AHR expression, impairing its protective effects. Our findings suggest that lower DNA methylation in COPD could disrupt mitochondrial function and cell death regulation, pointing to AHRR's role in COPD pathogenesis and offering potential for future therapeutic strategies.

Glutathione (GSH) is one of the antioxidants that protect the airway epithelium from damage, with its synthesis regulated by glutamate-cysteine ligase (GCLC). GSH levels decrease quickly in the lungs, plasma, and liver following cigarette smoke exposure in both mice and humans.

Cigarette smoke-induced hypermethylation of the GCLC promoter is linked to the onset and progression of COPD. This finding suggests that developing demethylation agents targeting GCLC hypermethylation could offer a new approach to COPD intervention.[29]

Specific changes in DNA methylation are linked to pollutants such as particulate matter (PM) and nitrogen dioxide (NO_2). The findings suggest that air pollution may influence disease development through changes in DNA methylation, providing insights into the biological mechanisms underlying pollution-related health risks. These epigenetic modifications are associated with genes involved in inflammation, oxidative stress, and cardiovascular and respiratory diseases.[30]

Song et al discovered that there is hypomethylation at 11 CpG sites in the Forkhead box protein A2 (FoxA2) promoter and 6 CpG sites in the SAM Pointed Domain Containing ETS Transcription Factor (SPDEF) promoter. The involvement of SPDEF and FoxA2 in mucus hypersecretion in COPD suggests that targeting these factors through epigenetic inhibition could provide new strategies for controlling mucus hypersecretion.[31]

Histone Modification

Various histone modifications, including acetylation, methylation, and phosphorylation, play significant roles in regulating gene expression. In COPD, smoking alters these histone marks, impacting inflammatory responses and disease progression.[21] An imbalance between histone acetylation and deacetylation affects nucleosomal structure during the transcription of inflammatory cytokine genes, which can result in altered gene expression profiles in smokers who are at risk of developing COPD.[18]

Histone Acetylation and Deacetylation

The release of pro-inflammatory cytokines depends on the activity of the transcription factor nuclear factor kappa B (NF-κB). This factor works in conjunction with co-activators like p300 and cAMP-response element binding protein (CREB), which possess histone acetyltransferase (HAT) activity, to promote gene transcription.[18]

Histone acetyltransferase enhances gene transcription by promoting the expression of pro-inflammatory factors involved in pathways such as mitogen-activated protein kinase (MAPK), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Signal Transducer And Activator Of Transcription (STAT), leading to inflammatory responses in epithelial cells. HAT activity modifies chromatin structure, making it more accessible to transcription factors and amplifying the inflammatory response seen in diseases like COPD.[1–4]

In the context of cigarette smoke exposure, a major risk factor for COPD, HAT-mediated acetylation exacerbates lung inflammation by increasing the expression of cytokines and chemokines. This highlights the potential for targeting HATs as a therapeutic strategy to reduce

chronic inflammation in respiratory diseases.[1–4]

HDACs are classified into several groups. They play a key role in gene regulation by removing acetyl groups from histones, resulting in chromatin condensation and transcriptional repression. Smoking has been shown to alter HDAC function, particularly reducing HDAC2 activity, which amplifies the inflammatory response and contributes to COPD progression.[18] Oxidative stress further exacerbates this effect by inhibiting HDAC2 activity. Chronic oxidative stress leads to both reduced HDAC2 activity and expression, which in turn enhances inflammation and corticosteroid resistance, complicating COPD management.[32]

Histone Methylation

Histone methylation plays a critical role in gene regulation, with specific patterns either activating or repressing gene expression. Altered methylation patterns in diseases like COPD can contribute to disease progression by modulating the expression of genes involved in inflammation and lung function.[1–3] Methylation of histone lysine or arginine residues leads to distinct, and sometimes even contradictory, functional outcomes. Additionally, the same lysine residues can exhibit varying degrees of methylation (mono-, di-, or tri-methylation), which can result in different biological effects.[33]

For instance, tri-methylation of histone H3 at lysine 4 (H3K4me3) is typically associated with active genes, whereas methylation at H3K9 and H3K27 is linked to gene repression. Research on the role of histone methylation in COPD remains limited. Significant association between the levels of H3K4me3 and increasing mRNA levels of Defensin Beta 1 (DEFB1), which correlates with the pathological progression of COPD.[34]

Furthermore, exposure to hypoxia, a potential trigger for COPD, led to an upregulation of both mRNA and protein levels of Protein Arginine Methyltransferase 2 (PRMT2) in mouse lung tissue.[35] Overall, histone methylation may play a role in COPD pathogenesis, warranting further investigation into the underlying mechanisms.

Histone Phosphorylation

Increased phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) in alveolar macrophages is a key driver of inflammatory responses in the lungs. The study by Gaffey et al investigates the presence of phosphorylated p38 MAPK in the lungs of COPD patients. The research reveals that levels of phosphorylated p38 MAPK are significantly elevated in the lung tissue of individuals with COPD compared to healthy controls. This increase is associated with heightened inflammatory responses and may contribute to the pathophysiology of COPD.[36]

This phosphorylation process leads to the production of inflammatory cytokines, especially in smokers with COPD. Cigarette smoke activates kinases that promote inflammatory gene

expression through histone phosphorylation. This histone modification facilitates transcription factor access to pro-inflammatory genes. Targeting kinase activation and histone phosphorylation could present potential therapeutic strategies to mitigate chronic inflammation in smokers with COPD, potentially improving disease management by reducing inflammation and slowing progression.[1–3]

The review by Ahmadi et al focuses on the role of p38 MAPK signaling contributes to key processes in COPD, including inflammation, apoptosis, and tissue remodeling. They highlight the pathway's involvement in exacerbating inflammatory responses and the progression of the disease. Additionally, the review evaluates various p38 MAPK inhibitors currently under investigation, emphasizing their potential to reduce inflammation and improve lung function in COPD patients.[37]

Histone Ubiquitination

The ubiquitin-proteasome system (UPS) plays a vital role in regulating protein degradation, particularly in the context of skeletal muscle dysfunction associated with COPD.[38,39] In COPD, especially among smokers, there is a disruption in the balance between muscle protein synthesis and degradation, leading to the loss of contractile proteins in the diaphragm and skeletal muscles.[39]

Activation of the UPS contributes to this imbalance by accelerating the breakdown of these proteins. The expression of pro-inflammatory cytokines is heightened in COPD, further promoting UPS activity and exacerbating muscle degradation. This increased UPS activity, particularly in degrading critical contractile proteins like myosin, significantly contributes to respiratory muscle weakness in COPD patients.[40]

Specifically, smoking upregulates Ubiquitin-specific proteases-19 (USP-19), a deubiquitinating enzyme, through the activation of p38 and extracellular-signal-regulated kinase (ERK)/MAPK pathways. This leads to skeletal muscle atrophy and a significant loss of myosin in the diaphragm, weakening respiratory function in COPD patients. Moreover, given the role of UPS in this process, it presents a potential therapeutic target for interventions aimed at preventing muscle atrophy and preserving muscle function in individuals with COPD.[38]

Noncoding RNA

The study by Ren et al explores the role of noncoding RNAs (ncRNAs) in the pathogenesis and potential treatment of COPD. NcRNAs, including microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), are shown to regulate key cellular processes such as inflammation, apoptosis, and oxidative stress, all of which contribute to COPD progression.[21]

miR-145 exerts a suppressive effect on the release of pro-inflammatory cytokines from airway smooth muscle cells in COPD patients by targeting SMAD Family Member 3 (SMAD3), a key downstream effector in the transforming growth factor

(TGF)-β signaling cascade.[41] By modulating ncRNA activity, it may be possible to develop new therapies aimed at slowing disease progression and improving patient outcomes.[21]

The abnormal expression of long noncoding RNAs (lncRNAs) has been shown to play a role in various diseases, such as COPD. LncRNA NNT-AS1 (NNT-AS1) was up-regulated in CSE-treated 16HBE cells, and its knockdown reversed CSE-induced effects on cell proliferation, apoptosis, inflammation, and airway remodeling, revealing its role in smoking-induced COPD through the miR-582-5p/FBXO11 pathway.[42]

Low expression levels of MCM3AP-AS1 are linked to an increased likelihood of COPD in smokers. COPD development involves airway remodeling, where abnormal proliferation of human bronchial smooth muscle cells (HBSMCs) plays a key role. The study found that MCM3AP-AS1 negatively regulates HBSMC proliferation, indicating its potential as a therapeutic target for COPD.[43] lncRNA COPDA1 enhanced the expression of MS4A1, leading to increased store-operated calcium entry in HBSMCs, which in turn stimulated the proliferation of smooth muscle cells and contributed to airway remodeling.[44]

EPIGENETIC THERAPEUTIC APPROACH OF COPD

Current and emerging therapeutic strategies aim to target epigenetic modifications in COPD. These approaches include agents that reverse or modulate epigenetic changes to mitigate inflammation and disease progression. A combined therapeutic approach utilizing DNMT inhibitors along with anti-inflammatory medications holds significant potential in the treatment of COPD. This strategy is promising because DNMT inhibitors target abnormal DNA methylation patterns, which are linked to inflammation and disease progression in COPD.[21]

By restoring normal gene expression, these inhibitors could reduce the chronic inflammatory response. When used alongside anti-inflammatory drugs, which directly suppress the inflammation, the combination could offer a more comprehensive treatment by addressing both the underlying epigenetic changes and the ongoing inflammatory processes, potentially slowing disease progression and improving patient outcomes.[21]

Diet and environmental factors influence epigenetic mechanisms involved in the pathogenesis of COPD, with nutrients playing a key role in regulating these mechanisms through natural phytochemicals that target signaling pathways in chronic respiratory diseases. Nutritional epigenomics (nutrigenomics) explores how nutrients affect health by modifying gene expression through epigenetic changes, such as DNA methylation and histone modifications, via 1-carbon metabolism.[45,46]

Antioxidants, vitamins, fiber, and dietary patterns have been shown to influence lung health and COPD progression by regulating inflammation,

oxidative stress, and carbon dioxide/oxygen balance. Antioxidant-rich foods, particularly fruits, are positively associated with improved lung function and reduced COPD-related respiratory symptoms and mortality.[47] Natural antioxidants like polyphenols, flavonoids, curcumin, resveratrol, green tea catechins, quercetin, and others show potential in preventing and treating COPD.[45]

A healthy dietary pattern, characterized by a high intake of fruits, vegetables, fish, and whole grains, is associated with a lower risk of COPD. In contrast, a Western diet high in cured and processed meats, red meat, preserved foods, and refined carbohydrates is linked to an increased risk of COPD and respiratory symptoms like coughing with phlegm. The Mediterranean diet, on the other hand, is associated with better lung function, improved spirometric parameters, and a lower prevalence of COPD.[45]

Curcumin, a compound found in turmeric (Curcuma longa), is known for its broad therapeutic effects and protective properties in various diseases. Studies have shown that curcumin can reduce proinflammatory cytokines like IL-1β, IL-6, IL-8, and TNF-α and has antioxidant effects.[48]

In a rat model of COPD induced by cigarette smoke, curcumin was found to block the mRNA expression of proinflammatory molecules (IL-8, MCP-1, MIP-2α) and modulate HDAC2 expression, which plays a role in inflammation. Cigarette smoke reduced HDAC2 expression and altered histone modifications, but curcumin reversed these changes. This suggests that curcumin can reduce inflammation and potentially restore corticosteroid resistance in COPD by modulating HDAC2 and histone modification.[48]

Quercetin, a flavonoid with anti-inflammatory and antioxidant properties, has shown promise in enhancing epithelial regeneration in COPD.[49] It negatively regulates matrix metalloproteinase (MMP) expression, which is crucial for extracellular matrix degradation and tissue damage in COPD. In vitro studies reveal that quercetin promotes the proliferation and differentiation of airway basal cells, aiding epithelial restoration. Its beneficial effects are linked to the modulation of HDAC activity, which influences MMP expression and improves disease outcomes.[50]

In an elastase/LPS mouse model, quercetin prevents COPD progression by downregulating MMPs through HDAC modulation, impacting signaling pathways related to cell proliferation and differentiation. By enhancing the expression of growth factors and cytokines essential for repair, quercetin emerges as a potential therapeutic strategy for COPD, contributing to better symptom management and lung function improvement.[50]

Theophylline restores HDAC activity and enhances steroid responsiveness in COPD macrophages. Theophylline, at low doses, was shown to increase HDAC activity in COPD macrophages, thereby

improving their responsiveness to corticosteroids. This suggests that theophylline may help overcome steroid resistance in COPD patients, potentially enhancing the efficacy of steroid treatments and reducing inflammation more effectively.[51]

This suggests that theophylline could be a valuable adjunctive treatment for improving steroid sensitivity and managing inflammation in COPD. The systematic review and meta-analysis by Shuai et al evaluated the effects of adding low-dose theophylline to inhaled corticosteroid (ICS) therapy in patients with COPD. The study assessed clinical outcomes such as lung function, exacerbation frequency, and quality of life. The results indicate that low-dose theophylline combined with ICS offers modest improvements in lung function and symptom control compared to ICS alone.[52]

However, the clinical significance of these benefits is limited, and theophylline's potential side effects, including its narrow therapeutic range, warrant cautious use. The study highlights the need for further research on the optimal use of this combination therapy in COPD management.[52]

CONCLUSION

Understanding the epigenetic landscape of COPD reveals critical insights into novel therapeutic avenues for this complex disease. DNA methylation and histone modifications significantly influence key cellular processes, including inflammation, cell cycle regulation, and apoptosis, which are central to COPD progression. Despite growing recognition of the role of epigenetic alterations in COPD, the underlying molecular mechanisms remain poorly defined. Therefore, advancing research in this area is crucial for unraveling these intricate pathways and developing targeted interventions that can reverse or mitigate epigenetic changes. Such therapeutic strategies hold the potential to significantly improve disease management and patient outcomes, making this an urgent priority in the future of COPD treatment.

REFERENCES

1. Zhang L, Valizadeh H, Alipourfard I, Bidares R, Aghebati-Maleki L, Ahmadi M. Epigenetic Modifications and Therapy in Chronic Obstructive Pulmonary Disease (COPD): An Update Review. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2020;17(3):333–42.
2. Agusti A, F. Vogelmeier C. GOLD 2024: a brief overview of key changes. Jornal Brasileiro de Pneumologia. 2023;49(6):e20230369.
3. Benincasa G, DeMeo DL, Glass K, Silverman EK, Napoli C. Epigenetics and pulmonary diseases in the horizon of precision medicine: a review. European Respiratory Journal. 2021;57(6):2003406.
4. Czarnecka-Chrebelska KH, Mukherjee D, Maryanchik S V., Rudzinska-Radecka M. Biological and Genetic

Mechanisms of COPD, Its Diagnosis, Treatment, and Relationship with Lung Cancer. Biomedicines. 2023;11(2):448.
5. World Health Organization. Projections of mortality and causes of death, 2015 and 2030. 2004.
6. Pandey R, Singh M, Singhal U, Gupta KB, Aggarwal SK. Oxidative/Nitrosative Stress and the Pathobiology of Chronic Obstructive Pulmonary Disease. Journal of Clinical and Diagnostic Research. 2013;7(3):580–8.
7. Rajendrasozhan S, Yao H, Rahman I. Current Perspectives on Role of Chromatin Modifications and Deacetylases in Lung Inflammation in COPD. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2009;6(4):291–7.
8. Feinberg AP. The Key Role of Epigenetics in Human Disease Prevention and Mitigation. New England Journal of Medicine. 2018;378(14):1323–34.
9. Qiu W, Baccarelli A, Carey VJ, Boutaoui N, Bacherman H, Klanderman B, et al. Variable DNA Methylation Is Associated with Chronic Obstructive Pulmonary Disease and Lung Function. Am J Respir Crit Care Med. 2012;185(4):373–81.
10. Corner J, Hopkinson J, Fitzsimmons D, Barclay S, Muers M. Is late diagnosis of lung cancer inevitable? Interview study of patients' recollections of symptoms before diagnosis. Thorax. 2005;60(4):314–9.
11. Li Y. Modern epigenetics methods in biological research. Methods. 2021;187:104–13.
12. Sundar IK, Rahman I. Gene expression profiling of epigenetic chromatin modification enzymes and histone marks by cigarette smoke: implications for COPD and lung cancer. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2016;311(6):L1245–58.
13. Barnes PJ. Mechanisms of development of multimorbidity in the elderly. European Respiratory Journal. 2015;45(3):790–806.
14. Clifford RL, Fishbane N, Patel J, MacIsaac JL, McEwen LM, Fisher AJ, et al. Altered DNA methylation is associated with aberrant gene expression in parenchymal but not airway fibroblasts isolated from individuals with COPD. Clin Epigenetics. 2018;10:32.
15. Joehanes R, Just AC, Marioni RE, Pilling LC, Reynolds LM, Mandaviya PR, et al. Epigenetic Signatures of Cigarette Smoking. Circ Cardiovasc Genet. 2016;9(5):436–47.
16. Bermingham ML, Walker RM, Marioni RE, Morris SW, Rawlik K, Zeng Y, et al. Identification of novel differentially methylated sites with potential as clinical predictors of impaired respiratory function and COPD. EBioMedicine. 2019;43:576–86.

17. Yang I V., Schwartz DA. Epigenetic Control of Gene Expression in the Lung. Am J Respir Crit Care Med. 2011;183(10):1295–301.
18. Wu DD, Song J, Bartel S, Krauss-Etschmann S, Rots MG, Hylkema MN. The potential for targeted rewriting of epigenetic marks in COPD as a new therapeutic approach. Pharmacol Ther. 2018;182:1–14.
19. Zong DD, Ouyang RY, Chen P. Epigenetic mechanisms in chronic obstructive pulmonary disease. Eur Rev Med Pharmacol Sci. 2015;19(5):844–56.
20. Shi Z, Chen Y, Pei Y, Long Y, Liu C, Cao J, et al. The role of cyclooxygenase-2 in the protection against apoptosis in vascular endothelial cells induced by cigarette smoking. J Thorac Dis. 2017;9(1):30–41.
21. Schamberger AC, Mise N, Meiners S, Eickelberg O. Epigenetic mechanisms in COPD: implications for pathogenesis and drug discovery. Expert Opin Drug Discov. 2014;9(6):609–28.
22. Barnes PJ, Adcock IM. Chronic Obstructive Pulmonary Disease and Lung Cancer: A Lethal Association. Am J Respir Crit Care Med. 2011;184(8):866–7.
23. Chen Y, Hanaoka M, Chen P, Droma Y, Voelkel NF, Kubo K. Protective effect of beraprost sodium, a stable prostacyclin analog, in the development of cigarette smoke extract-induced emphysema. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2009;296(4):L648–56.
24. Monick MM, Beach SRH, Plume J, Sears R, Gerrard M, Brody GH, et al. Coordinated changes in AHRR methylation in lymphoblasts and pulmonary macrophages from smokers. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2012;159B(2):141–51.
25. Armstrong DA, Chen Y, Dessaint JA, Aridgides DS, Channon JY, Mellinger DL, et al. DNA Methylation Changes in Regional Lung Macrophages Are Associated with Metabolic Differences. Immunohorizons. 2019;3(7):274–81.
26. Morrow JD, Cho MH, Hersh CP, Pinto-Plata V, Celli B, Marchetti N, et al. DNA methylation profiling in human lung tissue identifies genes associated with COPD. Epigenetics. 2016;11(10):730–9.
27. Peng H, Guo T, Chen Z, Zhang H, Cai S, Yang M, et al. Hypermethylation of mitochondrial transcription factor A induced by cigarette smoke is associated with chronic obstructive pulmonary disease. Exp Lung Res. 2019;45(3–4):101–11.
28. Chen Q, Nwozor KO, van den Berge M, Slebos DJ, Faiz A, Jonker MR, et al. From Differential DNA Methylation in COPD to Mitochondria: Regulation of AHRR Expression Affects Airway Epithelial Response to Cigarette Smoke. Cells. 2022;11(21):3423.

29. Cheng L, Liu J, Li B, Liu S, Li X, Tu H. Cigarette Smoke-Induced Hypermethylation of the GCLC Gene Is Associated With COPD. Chest. 2016;149(2):474–82.
30. Lee MK, Xu CJ, Carnes MU, Nichols CE, Ward JM, Kwon SO, et al. Genome-wide DNA methylation and long-term ambient air pollution exposure in Korean adults. Clin Epigenetics. 2019;11(1):37.
31. Song J, Heijink IH, Kistemaker LEM, Reinders-Luinge M, Kooistra W, Noordhoek JA, et al. Aberrant DNA methylation and expression of SPDEF and FOXA2 in airway epithelium of patients with COPD. Clin Epigenetics. 2017;9:42.
32. Barnes PJ. Targeting histone deacetylase 2 in chronic obstructive pulmonary disease treatment. Expert Opin Ther Targets. 2005;9(6):1111–21.
33. Mosammaparast N, Shi Y. Reversal of Histone Methylation: Biochemical and Molecular Mechanisms of Histone Demethylases. Annu Rev Biochem. 2010;79:155–79.
34. Andresen E, Günther G, Bullwinkel J, Lange C, Heine H. Increased Expression of Beta-Defensin 1 (DEFB1) in Chronic Obstructive Pulmonary Disease. PLoS One. 2011;6(7):e21898.
35. Yildirim AO, Bulau P, Zakrzewicz D, Kitowska KE, Weissmann N, Grimminger F, et al. Increased Protein Arginine Methylation in Chronic Hypoxia. Am J Respir Cell Mol Biol. 2006;35(4):436–43.
36. Gaffey K, Reynolds S, Plumb J, Kaur M, Singh D. Increased phosphorylated p38 mitogen-activated protein kinase in COPD lungs. European Respiratory Journal. 2013;42(1):28–41.
37. Ahmadi A, Ahrari S, Salimian J, Salehi Z, Karimi M, Emamvirdizadeh A, et al. p38 MAPK signaling in chronic obstructive pulmonary disease pathogenesis and inhibitor therapeutics. Cell Communication and Signaling. 2023;21(1):314.
38. Liu Q, Xu W, Luo Y, Han F, Yao X, Yang T, et al. Cigarette smoke-induced skeletal muscle atrophy is associated with up-regulation of USP-19 via p38 and ERK MAPKs. J Cell Biochem. 2011;112(9):2307–16.
39. Degens H, Gayan-Ramirez G, van Hees HWH. Smoking-induced Skeletal Muscle Dysfunction. From Evidence to Mechanisms. Am J Respir Crit Care Med. 2015;191(6):620–5.
40. Stockbridge EL, Kabani FA, Gallups JS, Miller TL. Ramadan and Culturally Competent Care: Strengthening Tuberculosis Protections for Recently Resettled Muslim Refugees. Journal of Public Health Management and Practice. 2020;26(5):E13–6.
41. O'Leary L, Sevinç K, Papazoglou IM, Tildy B, Detillieux K, Halayko AJ, et al. Airway smooth muscle inflammation is regulated by micro RNA -145 in COPD. FEBS Lett. 2016;590(9):1324–34.
42. Mei J, Zhang Y, Lu S, Wang J. Long non-coding RNA NNT-AS1 regulates

proliferation, apoptosis, inflammation and airway remodeling of chronic obstructive pulmonary disease via targeting miR-582-5p/FBXO11 axis. Biomedicine & Pharmacotherapy. 2020;129:110326.

43. Zhao K, Tu C, Liang K, Li Y, Yu Y. Long noncoding RNA MCM3AP antisense RNA 1 is downregulated in chronic obstructive pulmonary disease and regulates human bronchial smooth muscle cell proliferation. Journal of International Medical Research. 2020;48(9):300060520935215.
44. Zheng M, Hong W, Gao M, Yi E, Zhang J, Hao B, et al. Long Noncoding RNA COPDA1 Promotes Airway Smooth Muscle Cell Proliferation in Chronic Obstructive Pulmonary Disease. Am J Respir Cell Mol Biol. 2019;61(5):584–96.
45. Marín-Hinojosa C, Eraso CC, Sanchez-Lopez V, Hernández LC, Otero-Candelera R, Lopez-Campos JL. Nutriepigenomics and chronic obstructive pulmonary disease: potential role of dietary and epigenetics factors in disease development and management. Am J Clin Nutr. 2021;114(6):1894–906.
46. Cherneva R V., Kostadinov D. Epigenetic targets for therapeutic approaches in COPD and asthma. Nutrigenomics – possible or illusive. Folia Med (Plovdiv). 2019;61(3):358–69.
47. Scoditti E, Massaro M, Garbarino S, Toraldo DM. Role of Diet in Chronic Obstructive Pulmonary Disease Prevention and Treatment. Nutrients. 2019;11(6):1357.
48. Gan X, Li C, Wang J, Guo X. Curcumin modulates the effect of histone modification on the expression of chemokines by type II alveolar epithelial cells in a rat COPD model. Int J Chron Obstruct Pulmon Dis. 2016;11:2765–73.
49. Han MK, Barreto TA, Martinez FJ, Comstock AT, Sajjan US. Randomised clinical trial to determine the safety of quercetin supplementation in patients with chronic obstructive pulmonary disease. BMJ Open Respir Res. 2020;7(1):e000392.
50. McCluskey ES, Liu N, Pandey A, Marchetti N, Sajjan U. Quercetin improves epithelial regeneration from airway basal cells of COPD patients. Res Sq [Preprint]. 2023. p. rs.3.rs3185241.
51. Cosio BG, Tsaprouni L, Ito K, Jazrawi E, Adcock IM, Barnes PJ. Theophylline Restores Histone Deacetylase Activity and Steroid Responses in COPD Macrophages. J Exp Med. 2004;200(5):689–95.
52. Shuai T, Zhang C, Zhang M, Wang Y, Xiong H, Huang Q, et al. Low-dose theophylline in addition to ICS therapy in COPD patients: A systematic review and meta-analysis. PLoS One. 2021;16(5):e0251348.

Literature Review

The Evolution of Transbronchial Lung Biopsy Guidance

Mohamad Fahmi Alatas, Asri Liqditta Bies*, Prasenohadi, Dicky Soehardiman, Wahju Aniwdyaningsih, Mia Elhidsi, Ginanjar Arum Desianti, Tina Reisa, Menaldi Rasmin

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta

Corresponding Author:
Asri Liqditta Bies | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Persahabatan General Hospital, Jakarta | biesasriliqdita@gmail.com

Submitted: January 15th, 2024
Accepted: March 3rd, 2025
Published: March 8th, 2025

Respir Sci. 2025; 5(2): 141-52
https://doi.org/10.36497/respirsci.v5i2.170

Abstract

Histological confirmation of lung lesions is necessary prior to determining further management. Imaging preparation is needed to find the biopsy site such as a computed tomography scan. Imaging helps to trace the position of lung lesions that are peripheral and not visualized by bronchoscope. However, along with the discovery of small lesions and peripheral location, two-dimensional imaging alone remains suboptimal. Therefore, to reach lung lesions peripherally would need to a guide through the bronchial. Subsequently, the method of guiding transbronchial biopsy evolved. Namely, real-time fluoroscopy, radial-probe endobronchial ultrasound, virtual bronchoscopy navigation and electromagnetic bronchoscopy navigation are guiding modalities with each of their advantages and disadvantages. Several biopsy modalities are used in combination to increase the accuracy of diagnosis. Careful analysis in planning and an understanding of the limitations and advantages of diagnostic modalities must be considered in deciding which method to choose.

Keywords: bronchoscopy, peripheral pulmonary lesions, transbronchial biopsy

INTRODUCTION

Lung cancer contributes 9.5% of all incidence of cancer of both sexes in Indonesia, leading into the second rank but first ranked of mortality.[1] For many years, lung biopsy was performed surgically. However, when solitary pulmonary nodules were routinely resected, it turned out that half of them were benign and did not require surgery with its side effects. This is why there is a demand for histological confirmation before surgery. The challenge is to find the path to the lesion because calculating the location of the lesion from an X-ray or computed tomography scan (CT scan) and trying to approach it only with an endoscopic view has a very low success rate.[2]

Real-time control of transbronchial biopsy under fluoroscopy showed better visualization. Although it provides good visualization, large radiation associated with duration exposure is a drawback. Thus, the development of transbronchial

biopsy techniques continues to occur in order to improve the accuracy of diagnosis.[2]

Bronchoscopy can be divided into diagnostic and therapeutic procedures. Diagnostic bronchoscopy has been mostly performed as a basic procedure by pulmonologists in proving lung lesions. Simple bronchoscopy procedures have been carried out in many hospitals, while advanced procedures are only done in referral hospitals. Another peripheral pulmonary lesion (PPL) biopsy is a transthoracic lung biopsy with the lesion attached to the chest wall. Currently, there are several guided biopsy methods for PPLs such as CT scan, fluoroscopy, radial probe endobronchial ultrasound (RP-EBUS), electromagnetic bronchoscopy navigation (EBN), and virtual bronchoscopy navigation (VBN).[3]

TRANSBRONCHIAL LUNG BIOPSY

Peripheral pulmonary lesion is non-directly visible through bronchoscopy. It is often an accidental finding while screening lung cancer with low-dose CT scans. The location, size of the lesion, and sampling technique play a role in the diagnostic result. Small PPL <2 cm gives a diagnostic yield of only 30%. While lesions >4 cm give a diagnostic yield of up to 80%.[2,3]

The positivity rate was reported to increase using advanced imaging and navigation techniques by up to 74% for small PPL <2 cm. Intuitively, bronchoscopists think that achieving good positivity depends on the proximity of the lesion to the airway, the angle at which it is located, and the number of samples taken.[2,3]

A meta-analysis by Rivera et al mentioned transbronchial needle aspiration biopsy (TBNA) in combination with TBB was superior to TBB alone. Operators usually estimate the three-dimensional bronchi regarding a two-dimensional planar axial section of the CT scan. Sometimes this method is less accurate for more peripheral bronchi than subsegmental bronchi. Diagnostic results depend not only on the size of the lesion but also on bronchus signs on CT scans, fluoroscopic visibility, and operator skills.[3]

Transbronchial lung biopsy (TBLB) is a biopsy procedure obtaining lung nodules by using flexible forceps positioned distally through a working channel of flexible bronchoscopy. The procedure can be obtained with or without guidance. Blind TBLB called for without guidance lung biopsy typically for lung parenchyma diffuse disease. This modality requires a unique technique and is not often used as it has considerable additional risks such as sensory feedback from a moderately sedated patient.[4]

Guided TBLB is depicted as a biopsy with imaging, such as fluoroscopy as confirmation precise position of biopsy tools through a working channel of a bronchoscope. The diagnostic yield increased by several specimen collections around 6-10 specimens. When performed with bronchial brushing and needle aspiration biopsy may increase the diagnostic yield. The success of lung

transplantation also has a role for transbronchial biopsy in determining cellular contraindications.[4]

Recently, a conventional TBLB refers to TBLB with CT scan guidance and confirmation under fluoroscopy. Peripheral pulmonary lesions, particularly beyond the sub-segmental bronchi, are more difficult than the central lesion. The bronchoscope and biopsy instrument passes through the bronchi and branches reaching the biopsy target. Therefore, innovation was carried out and developed because the diagnostic value of conventional transbronchial biopsy is not good, especially in very peripheral lesions. Plus, the lesion is less than two centimeters.[4,5]

Indications and Contraindication

A transbronchial lung biopsy can be performed in focal and diffuse lung diseases. High-resolution computed tomography (HRCT) and CT scan findings in diffuse lung pathology may be an indication for a transbronchial lung biopsy. However, clinical correlation and other non-invasive diagnostic considerations should be made beforehand. In focal lung lesions with a peripheral location, CT scan-guided identification and localization can aid in identification. The use of the procedure together with fluoroscopy and the development of navigation technologies such as VBN, ENB, and cone beam computed tomography can increase the positivity rate of TBB.[2,6]

The most common complications of the TBLB procedure were bleeding (<4%), pneumothorax (<2%), and death (<0.05%). The risk of bleeding can increase to 89% in patients taking anticoagulant drugs, so if a TBLB is still needed, anticoagulant administration should be stopped five days before the procedure. Severe hypoxemia despite oxygen administration, unstable cardiovascular status, no patient consent, and unavailability of trained resources and equipment are absolute contraindications.[2,4]

Meanwhile, relative contraindications are a cough that is not controlled with drugs, hypercoagulation, thrombocytopenia, renal failure, large pulmonary blisters, and malformations of blood vessels at the site of the lesion. Pulmonary hypertension is still debated as a contraindication.[2,4]

Procedure Preparation Guidance

Kurimoto defines the bronchial tree reading method in CT scans into three steps. The first step is to observe the lung field from the apex to the diaphragm and then determine the lesion's location to be the biopsy's target. The second step follows the outline of the bronchial tree via the axial section of the lung window. Follow from the trachea to the carina then move to the right and left main bronchi and their branches. Observations following the bronchial route to the target lesion for biopsy can be repeated to confirm the location. For example, the lesion is located on B5a and B5b mainly occupying B5b as seen in Figure 1.[7]

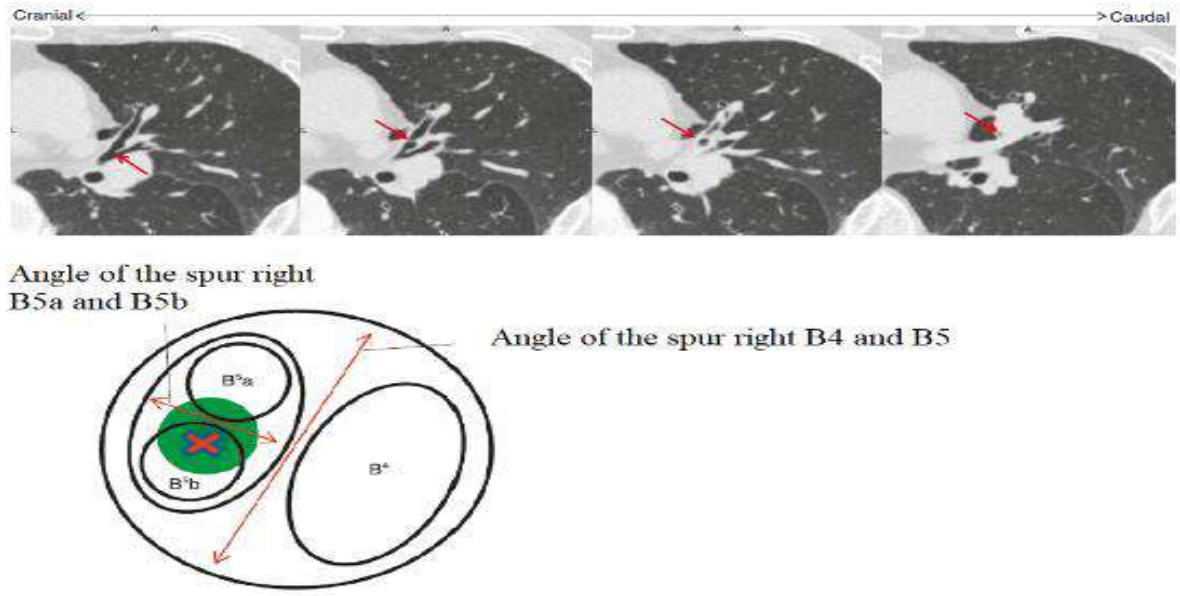


Figure 1. Middle lobe bronchial branch[7]

Biopsy was directed at B5b. On a CT scan, the first branches of the middle lobe bronchus go to B4 and B5. After finding the branching angles of B4 and B5 then follow them in a medial direction. An axial CT scan is followed caudally until a biopsy target lesion is seen.[7]

The third step is to rotate and reverse the position of the CT scan image so that the position of the lesion is in the same direction as the bronchoscope visualization. For example, a lesion located in the middle lobe, lingula, right and left lower lobe makes it easy to read the location by reversing the CT scan image. For the upper lobe left lung lesion rotate 90^0 clockwise axial lung window CT scan then follow the left main bronchus from caudal to cranial. The bronchoscope visualization will be similar to the direction of the CT scan.[7,8]

A systematic review and meta-analysis in 2018 showed that the guidance of bronchial signs on CT scans correlated with better diagnostic values compared to those without bronchial signs. However, there are some confounding factors such as the size and distance of the lesion from the hilum as a determinant of TBLB.[7,8]

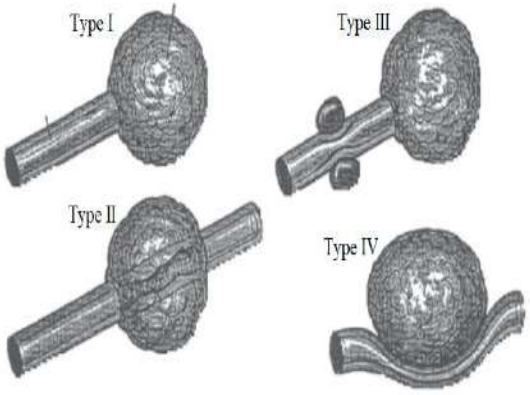


Figure 2. Bronchus sign classification by Tsuboi[2]

Tsuboi classified bronchial signs into four types (Figure 2). The first type is the bronchial lumen over to the lesion. Type two, where the lesion grows to enfold the bronchi into the lumen. The biopsy technique for type 2 involves inserting forceps deep enough into the lesion.[2,9]

Type three is bronchi compressed by the lesion so that the bronchial lumen is

narrowed and there is no infiltration of the lesion into the bronchial lumen. This type is impossible to reach the lesion so it often gives a negative result. Type four is narrowed proximal bronchial lumen due to infiltration of the lesion into the bronchial sub-epithelium or due to suppression of lymph nodes while the lesion is distal to the bronchial lumen. This type makes it difficult for the forceps to enter the distal lumen.[2,9]

TRANSBRONCHIAL LUNG BIOPSY WITH FLUOROSCOPY GUIDANCE

Fluoroscopy is designed to display the shadow of the body's organs at the actual time. Important components of fluoroscopy are X-ray tubes and shadowing devices that are connected to the monitor screen. A common type of fluoroscopy is the C-Arm type, an arm-shaped letter c. Fluoroscopy C-arm consists of an x-ray tube beneath the patient's table and a shadow capture above the patient's table. This position is called the under-couch position and provides the least radiation exposure.[2]

Radiation hazard effects on patients are derived from the light fraction absorbed into the body's organs while health workers come from scattered radiation. The modern fluoroscopy system has an element that can minimize the light fraction without reducing the quality of the image. Measurement several times becomes a method that can reduce radiation exposure during biopsy procedures.[2]

Fluoroscopy serves to confirm forceps instruments to generate good diagnostic results. The operator performs bronchial inspection and its branches. This is to see endobronchial abnormalities while determining the location of the biopsy according to the CT scan guidance. The flexible bronchoscopy is then directed to the intended segmental bronchus. Furthermore, forceps are inserted into the bronchoscope through a working channel.[2,3]

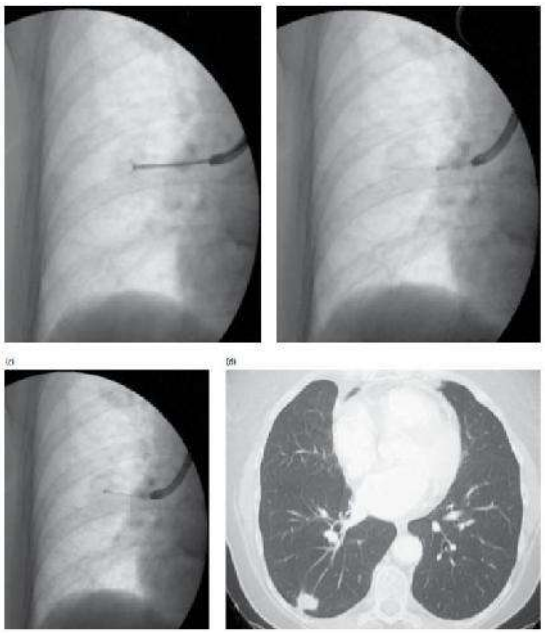


Figure 3. Biplane fluoroscopy to obtain lung specimens from selected areas[2]

Once the forceps have been seen distally from the working channel and precisely in the right subsegmental bronchi, fluoroscopy is activated to confirm the position. Forceps then gently push forward until resistance to confirm the distal of the bronchus branch. Forceps retracted around one centimeter for the space to open the forceps' jaw. Then gently push forward the open jaw forceps and grip for sampling for a while to

minimize bleeding. Forceps are then pulled with the technique of turning the bronchoscope. Biplane fluoroscopy can be seen in Figure 3. At the end of the biopsy, it is necessary to do a fluoroscopy to confirm pneumothorax as a complication.[2,3]

TRANSBRONCHIAL LUNG BIOPSY WITH RADIAL PROBE ENDOBRONCHIAL ULTRASOUND

Radial probe endobronchial ultrasonography (RP-EBUS) is a flexible catheter with a straight-shaped probe ultrasonography at the distal end of the catheter that can be rotated 360^0 to provide a circular sonographic picture. This tool is widely used to confirm the location of PPL before carrying TBLB, especially without a clear bronchus sign on the CT scan. The size of the RP-EBUS with an outer diameter of 1.4 mm is very small so it can easily reach the most peripheral bronchi branch.[10,11]

The position of RP-EBUS in the middle of the lesion as shown in Figure 4b gives a better diagnostic value than the adjacent or proximal position of the lesion Figure 4c. The positivity rate reached 86.7%. Several factors that affect the diagnostic yield of RP-EBUS have been identified including lesions and the location of the lesion as well as the location of the radial probe in relation to the lesion.[10,11]

The advantage of RP-EBUS guidance is the ability to accurately and in real-time identify PPL. The operator can observe the position of the probe within the lesion, adjacent to the lesion, or away from the lesion. When inspecting with RP-EBUS, if the bronchi are in or next to the lesion, then a biopsy guided by the EBUS guide sheet (GS) can produce good diagnostic value with minimal complications.[2,10]

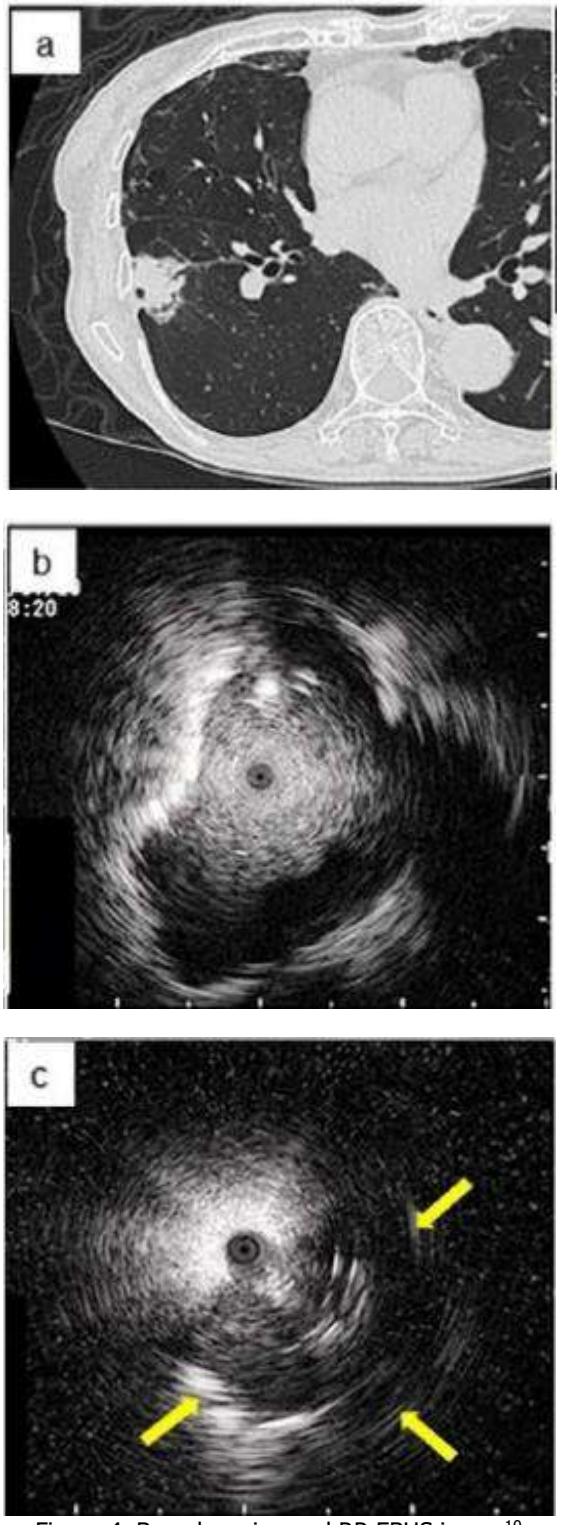


Figure 4. Bronchus sign and RP-EBUS image[10]

The key to this method is ensuring that the bronchoscope remains in its last position while the RP-EBUS is visualizing the target lesion for the biopsy. A plastic sheath called the GS makes it even easier for the forceps to reach the lesion when the radial probe is removed from the working channel.[2,10]

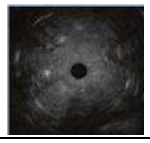
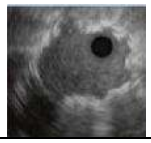
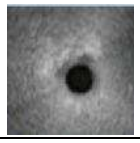
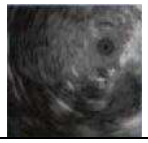
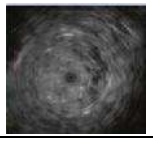
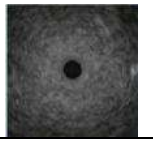
Observe endobronchial in three distances when bronchoscopy visualization showed abnormalities. Distance view to observe the condition of the surrounding bronchial mucosa. Intermediate view to observe the distribution of blood vessels using narrow-band imaging (NBI) features. Close view to observe the pattern of blood vessels. When the lesion is visualized with EBUS, the entire lesion is scanned by moving the probe from distal to proximal. Observe the structures within the lesion, such as echo view, vascular structure, and hyperechoic line boundaries.[2]

Classification of EBUS images is divided into three types. Type I is a homogeneous appearance divided into types Ia and Ib. Type Ia is a homogeneous appearance with patent blood vessels without compression. This type is thought to be an acute inflammation such as pneumonia. Type Ib is a homogeneous appearance without a blood vessel appearance. This type is thought to be chronic inflammation.[7]

Type II is a hyperechoic appearance inside the lesion divided into type IIa and IIb. Type IIa is hyperechoic without blood vessels and type IIb is hyperechoic with blood vessels. Type III is a heterogeneous appearance divided into types IIIa and IIIb. Type IIIa is a heterogeneous appearance spread linearly as if the bronchial lumen is compressed. Type IIIb is a non-linear heterogeneous appearance with a presumably poorly differentiated solid lesion.[7] This classification can be seen in Table 1.

Peripheral lesions that are not visualized on RP-EBUS have a low diagnostic yield when the biopsy is performed without other guidance. Another cause of the non-visible PPL is its location in the upper lobe, so it is difficult for GS to reach. Another cause is beyond the peripheral location close to the visceral pleura so the GS cannot reach until the smallest endobronchial.[11,12]

Table 1. The classification of EBUS images[7]

Type	**I**		**II**		**III**	
Internal echo	Homogeneous		Hyperechoic points		Heterogeneous	
Subtype	Ia	Ib	IIa	IIb	IIIa	IIIb
Open vessel	o	---	---	o	---	---
Hyperechoic linear echo	o	---	---	---	o	---
EBUS						

Xu et al revealed similar results to the study by Yamada et al, RP-EBUS TBB guidance diagnostic results depending on the position of the probe in the lesion. If the position of the probe is in the lesion it will give the best results compared to a position near or even far from the lesion. Guidance RP-EBUS coupled with GS is to provide the best diagnostic results with minimal complications.[11,12]

VIRTUAL BRONCHOSCOPY NAVIGATION

Virtual navigation bronchoscopy is a three-dimensional bronchoscopy method with virtual guidance of the bronchial route and its branches to reach the target biopsy lesion. Virtual navigation is carried out using software that has been applied to the system. The procedure of VBN consists of planning and guidance. The planning phase is the process before bronchoscopy by preparing virtual images of the bronchi and their branches to the target lesion for the biopsy. The guidance phase is the procedure of virtually directing the bronchoscope to the lesion. Currently, several navigation system products can be used by Japanese manufacturers (Bf-NAVI®) and the United States (LungPoint® and DirectPath®).[13,14]

Image from DirectPath® (Figure 5), an axial lung window CT scan shows the target location in the right eighth segment and is marked with a red circle. The bronchi and their branches are extracted by the system at the planning stage and shown in blue lines. The additional bronchial tree can be extracted manually. The blue line in the bronchial tree is the virtual route to the target lesion. The yellow circle represents the tip of the virtual bronchoscope. The green line extending from the yellow circle represents the virtual bronchoscope direction. On the left side of the image is a screen view of a virtual bronchoscope which can be compared with the view of a real bronchoscope. In this case, the figure shows the fifth generation of the bronchial tree and the blue line goes to the right B8aiiqy.[13,14]

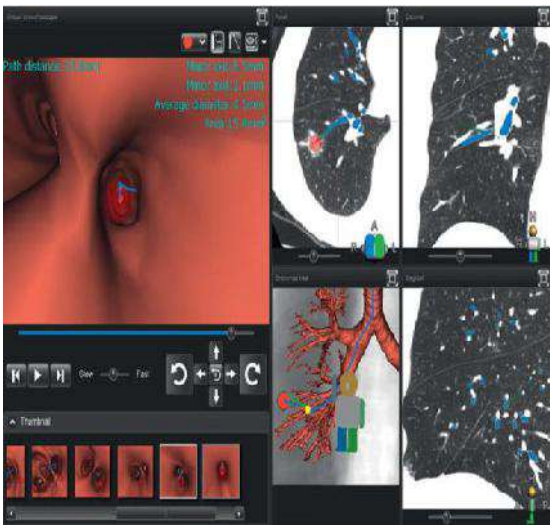


Figure 5. Virtual bronchoscopy navigation image[15]

A prospective randomized controlled trial concluded that the diagnostic value is up to 80% in small PPL measuring less than 30 mm in combination with VBN and RP-EBUS guidance. Several factors have yet to be proven between the positivity of the diagnostic results and virtual navigation guidance. These factors are the difference in lung volumes when holding a full inspiratory breath when a CT scan was performed. Meanwhile, when bronchoscopy is performed, the breathing condition is spontaneous so that

navigational discrepancies can occur, such as the normal narrowing of the bronchi during the breathing process.[13]

ELECTROMAGNETIC BRONCHOSCOPY NAVIGATION GUIDANCE

The first attempt at EBN in humans was in 2006.[14] Electromagnetic bronchoscopy navigation is a three-dimensional virtual navigation method of bronchial trees based on CT scan images. An electromagnetic sensor is attached to the distal bronchoscope through the working channel. A flat board is placed under the patient's bed cushion to emit electromagnetic waves, ensuring the biopsy target lesion will be captured in a square prism.[11,16]

The EBN method is not only useful for very peripheral lesions but also for small central lesions. Currently, there are two electromagnetic navigation software, namely superDimension® and SPiNDrive®. In principle, the EBN navigation system is like airplane navigation. The EBN guidance method consists of two stages consist of planning and procedures.[11,16]

Successful of the procedure depends on a good planning stage. The software reconstructs a three-dimensional view which is an axial, coronal, and sagittal view based on the CT scan results. The operator controls the bronchoscope according to virtual endobronchial guidance while comparing the actual view. The path to the target biopsy lesion is then determined by means of a cross. The planning stage data that has been made is then stored. At the procedure stage, the bronchoscope is directed toward the lesion then the guide sheet and locatable guide are inserted into the working channel. A locatable guide will provide position data to the system.[16]

A meta-analysis study in 2014 showed that EBN represents 65% of diagnostic value. Several factors contributed to the higher value such as the lesion size of more than 30 mm and the presence of bronchial signs. Pneumothorax occurs in around 3.1%, and bleeding with mild to moderate variations of around 1.6% are complications of the EBN method.[11]

Data collected in Hong Kong in 2019 shows that the diagnostic value of BNE is higher for lesions not visualized with RP-EBUS or fluoroscopy. One of the weaknesses of the EBN method is the high operational costs. Therefore, best planning is needed especially for a small probability of diagnostic value.[17]

OTHER TRANSBRONCHIAL LUNG BIOPSY GUIDANCE

The latest innovations in achieving biopsy target lesions are bronchoscopy trans-parenchymal nodule access (BTPNA)/transbronchial access tool (TBAT). A clinical trial that has been carried out since 2018, EAST-2 assessed the benefits and safety of the BTPNA method. The first human case report was by Herth and colleagues.[11,18]

Herth demonstrated sampling using a combination of Archimedes guidance and

fluoroscopy, although some samples were unable to see nodules by fluoroscopy giving the best diagnostic value of 83%. The BTPNA method can be used for lesions that are more centrally located or without bronchial signs.[11,18]

The BTPNA technique creates a path to a peripheral lesion through the lung parenchyma. This technique is integrated with Archimedes. Archimedes is a VBN system integrating bronchoscopy, CT scan data, and continuous fluoroscopy views to generate real-time airway views in a three-dimensional construct. A coring needle punctures the planned entry based on BTPNA guidance and then is dilated by a balloon catheter. The blunt dissection style sheath is inserted into the biopsy target. The BTPNA method increases the ability to access peripheral lung lesions with bronchoscopy. However, further research is still needed to assess its diagnostic positivity and safety.[11,18]

Robotic bronchoscopy is now being developed. This guidance was first performed in humans by Fielding et al. The advantage of robotic bronchoscopy is that it maintains the stable position of the flexible bronchoscope when peripheral lesions are visualized so that the lesion can be seen continuously and facilitates biopsy. There were several clinical trials of robotic bronchoscopy for the diagnosis of PPLs, including NCT04182815 and NCT04740047. Those clinical trials had been completed but are still in review to be published.[11,19]

CONCLUSION

Various transbronchial biopsy guidance continues to be developed to achieve the best diagnostic results for PPL. Pre-procedure planning following guidance are the two common steps. The diagnostic results are higher if there are bronchial signs at the pre-procedure stage based on a chest CT scan. Careful analysis in planning and an understanding of the limitations and advantages of diagnostic modalities must be considered in deciding which method to choose

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
2. Wang KP, Mehta AC, Turner JF. Flexible Bronchoscopy. 4th ed. Wiley-Blackwell; 2020.
3. Livi V, Barisione E, Zuccatosta L, Romagnoli M, Praticò A, Michieletto L, et al. Competence in navigation and guided transbronchial biopsy for peripheral pulmonary lesions. Panminerva Med. 2019;61(3):280–9.
4. Küpeli E, Feller-Kopman D, Mehta AC. Diagnostic Bronchoscopy. In: Murray and Nadel's Textbook of Respiratory Medicine. Elsevier; 2016. p. 372-382.e5.
5. Ost DE, Ernst A, Lei X, Kovitz KL, Benzaquen S, Diaz-Mendoza J, et al.

Diagnostic Yield and Complications of Bronchoscopy for Peripheral Lung Lesions. Results of the AQuIRE Registry. Am J Respir Crit Care Med. 2016;193(1):68–77.
6. Wahidi MM, Rocha AT, Hollingsworth JW, Govert JA, Feller-Kopman D, Ernst A. Contraindications and Safety of Transbronchial Lung Biopsy via Flexible Bronchoscopy. Respiration. 2005;72(3):285–95.
7. Kurimoto N, Morita K. Bronchial Branch Tracing. Springer Singapore; 2020. 4–18 p.
8. Ali MS, Sethi J, Taneja A, Musani A, Maldonado F. Computed Tomography Bronchus Sign and the Diagnostic Yield of Guided Bronchoscopy for Peripheral Pulmonary Lesions. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2018;15(8):978–87.
9. Imabayashi T, Matsumoto Y, Uchimura K, Furuse H, Tsuchida T. Computed Tomography Bronchus Sign Subclassification during Radial Endobronchial Ultrasound-Guided Transbronchial Biopsy: A Retrospective Analysis. Diagnostics. 2023;13(6):1064.
10. Kurihara Y, Tashiro H, Takahashi K, Tajiri R, Kuwahara Y, Kajiwara K, et al. Factors related to the diagnosis of lung cancer by transbronchial biopsy with endobronchial ultrasonography and a guide sheath. Thorac Cancer. 2022;13(24):3459–66.
11. Ishiwata T, Gregor A, Inage T, Yasufuku K. Bronchoscopic navigation and tissue diagnosis. Gen Thorac Cardiovasc Surg. 2020;68(7):672–8.
12. Herth FJF, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. European Respiratory Journal. 2002;20(4):972–4.
13. Ernst A, Anantham D. Bronchus Sign on CT Scan Rediscovered. Chest. 2010;138(6):1290–2.
14. Schwarz Y, Greif J, Becker HD, Ernst A, Mehta A. Real-Time Electromagnetic Navigation Bronchoscopy to Peripheral Lung Lesions Using Overlaid CT Images. Chest. 2006;129(4):988–94.
15. Asano F, Eberhardt R, Herth FJF. Virtual Bronchoscopic Navigation for Peripheral Pulmonary Lesions. Respiration. 2014;88(5):430–40.
16. Leong S, Ju H, Marshall H, Bowman R, Yang I, Ree AM, et al. Electromagnetic navigation bronchoscopy: A descriptive analysis. J Thorac Dis. 2012;4(2):173–85.
17. Cheng SL, Chu CM. Electromagnetic navigation bronchoscopy: the initial experience in Hong Kong. J Thorac Dis. 2019;11(4):1697–704.
18. Harzheim D, Sterman D, Shah PL, Eberhardt R, Herth FJF. Bronchoscopic Transparenchymal Nodule Access: Feasibility and Safety in an Endoscopic Unit. Respiration. 2016;91(4):302–6.
19. Giri M, Dai H, Puri A, Liao J, Guo S. Advancements in navigational bronchoscopy for peripheral

pulmonary lesions: A review with special focus on virtual bronchoscopic navigation. Front Med (Lausanne). 2022;9:989184.

AUTHOR INDEX

A

A Farih Raharjo 72

Aditya Wirawan 126

Ahmad Rusdan H Utomo 99

Arie Zainul Fatoni 62

Asri Liqditta Bies 141

B

Budhi Antariksa 126

D

Derallah A Lindra 99

Dewi Behtri Yanifitri 92

Dicky Soehardiman 141

E

Endang Purwaningsih 99

F

Faisal Yunus 99

Fanny Fachrucha 115

G

Ginanjar Arum Desianti 141

H

Hario Baskoro 126

Harman Prayitno 62

I

I Wayan Pande Adhyaksa 115

J

Jatu Aphridasari 72

M

Makrup E Harahap 99

Menaldi Rasmin 141

Mia Elhidsi 141

Mohamad Fahmi Alatas 141

N

Naohisa Matsumoto 126

Nurima Diyah Puji Hastuti 62

P

Prasenohadi 141

R

Rahmi Hayati 92

Rania Imaniar 126

R

Rezky Ahmad Isdiyanta 82

S

Sandy Kurniawan 72

Siti Chandra Widjanantie 82

T

Tina Reisa 141

Tri Wahju Astuti 62

Tutug Kinasih 126

W

Wahju Aniwdyaningsih 141

Y

Yani Jane Sugiri 62

Yunita Arliny 92

SUBJECT INDEX

A

Activities of daily living 82, 87

Alpha Klotho gene 99, 102

Anti-TB Drugs 92-97

B

Bronchoscopy 141-142, 145, 147-150

C

CADR 92-93, 95-97

Chronic obstructive pulmonary disease 126

Coinfection 62-71

COPD 99-105, 107-111

COVID-19 62-66, 68-71

Cutaneous Adverse Drug Reaction 92

D

DNA methylation 126-131, 134, 136

Drug-resistant tuberculosis 72-73, 78

E

Epigenetics 126-128

H

Histone modifications 126-128, 131, 134-136

HRQoL 72-75, 77-79

Hydropneumothorax 82-84, 86-89

I

Infectious disease 83

Interstitial lung abnormalities (ILA) 115-124

L

Length of stay 62

M

Mortality 62-63, 68, 70-71

P

People living with HIV/AIDS (PLHIV) 92-93

Peripheral pulmonary lesions 141, 143

Polymorphism 99-104, 107-111

Prevalence 115-117, 119-120

R

Rehabilitation 82-85, 87-89

Risk factors 115, 117, 122-123

T

Therapeutic strategies 126, 129-130, 133-136

Transbronchial biopsy 141-143, 150

Treatment 115, 119, 122

Tuberculosis 82-84, 86-87, 92-93, 96