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Original Article

# Differences In Interleukin-6 and Liver Enzyme Level Based On Clinical Severity of COVID-19 Patients at Dr. M. Djamil General Hospital, Padang

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## Abstract

**Background:** COVID-19 pathogenesis involves the release of proinflammatory cytokines and chemokines, known as a "cytokine storm." Interleukin-6 (IL-6) plays a key role in initiating cytokine storms. Cytokine storm causes multiple organ complications. Liver injury affects 14% to 53% of COVID-19 patients and is manifested by increased liver enzymes. This study evaluated differences in IL-6 and liver enzyme levels based on clinical severity in COVID-19 patients.

**Method:** A retrospective cross-sectional study was conducted. COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang, from January 1, 2021, to December 31, 2021, and who met the inclusion and exclusion criteria, were the research subjects. The Kruskal-Wallis test was performed to analyze differences in IL-6, SGOT, and SGPT levels based on clinical severity.

**Results:** Most participants (42.06%) were under 50 years old, half were female (56.15%), obesity was the most common comorbidity (41.39%), and moderate severity was most common (42.06%). The majority of the subjects, 87.47%, had elevated IL-6 levels (≥7 pg/mL). SGOT levels of ≥32 IU/L (46.76%) and SGPT levels of ≥31 IU/L (41.39%) were found in less than half of the subjectsClinical severity was significantly associated with IL-6 levels, resulting in a significant difference in IL-6 levels ($P<0.05$). The clinical severity of COVID-19 patients at Dr. M. Djamil General Hospital, Padang, resulted in a significant difference in SGOT and SGPT levels ($P<0.05$).

**Conclusion:** IL-6 levels differed based on clinical severity in COVID-19 patients. SGOT and SGPT levels also differed by clinical severity.

**Keywords:** clinical severity, COVID-19, IL-6, liver enzyme

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) is a threat to public health globally.[1,2] The spectrum of clinical presentations of the disease ranges from asymptomatic and mild-to-moderate to

severe, life-threatening illness. Coronavirus disease 2019 causes respiratory problems such as pneumonia and can develop into Acute Respiratory Distress Syndrome (ARDS), septic shock and multi-organ dysfunction, including the liver, kidneys, and heart.[2]

Interleukin-6 (IL-6) is the primary initiator of cytokine storms.[3] There has been research to determine the benefits of the initial IL-6 examination as a predictor of the severity of COVID-19 disease. According to Liu et al and Gubernatorova et al, IL-6 levels are an important factor in predicting the progression of COVID-19 infection.[4,5] Herold et al investigated the predictive value of various cytokines and concluded that IL-6 is the best predictor of COVID-19 disease progression, outperforming C-reactive protein (CRP) and other inflammatory markers.[6]

Cytokine storms can lead to complications in organs other than the lungs, such as the heart, kidneys, gastrointestinal tract, and liver.[2,6] Liver injury occurs in 14% to 53% of COVID-19 patients and is characterized by elevated hepatic enzyme levels of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and elevated bilirubin.[7]

However, the exact mechanism of liver damage remains unclear. Bourgonje et al concluded that liver damage in COVID-19 can occur through a variety of mechanisms, including hepatotoxicity from antiviral drugs and direct viral infection of liver cells and bile duct cells via angiotensin-converting enzyme 2 (ACE2), which is a SARS-CoV-2 receptor.[8] Another mechanism is hepatic cell ischemia caused by cytokine storms.

McConnell et al first reported a link between IL-6, hyperinflammation, and liver injury in COVID-19 patients, which found that higher IL-6 and coaguolpathy were associated with liver injury in COVID-19 patients.[9] Da et al also stated that liver injury in COVID-19 is related to the severity of COVID-19 and hyperinflammation, specifically an increase in inflammatory markers such as IL-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin.[10] Ponziani et al discovered a correlation between abnormal liver function tests and IL-6 levels, proving that COVID-19 liver injury was caused by systemic inflammation.[11]

Based on this background, this study aims to describe the differences in IL-6 and liver enzyme levels based on the clinical severity of COVID-19 patients at Dr. M. Djamil General Hospital, Padang.

## METHOD

This was a retrospective cross-sectional study. The study was carried out at Dr. M. Djamil General Hospital, Padang, from April 2022 to November 2022. COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang, between January 1 and December 31, 2021, who had IL-6, SGOT, and SGPT test results, complete medical records including age, gender, and comorbidities, and were aged ≥18 years, were included. Exclusion criteria included patients with autoimmune diseases

(rheumatoid arthritis, systemic lupus erythematosus/SLE, rheumatic heart disease, primary Sjogren's syndrome, fibrous bone dysplasia, juvenile idiopathic arthritis/JIA, and uveitis), chronic inflammation (Erdheim's disease, Chester, Behcet's syndrome, systemic sclerosis, large cell arteritis), malignancy (ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bone cancer, hematologic cancers, pancreatic, lung, liver, and lymphatic cancers, hepatoma), post-organ transplantation, hepatitis, chronic liver disease.

## RESULT

There were 447 subjects in this study. Table 1 shows the characteristics of COVID-19 patients treated at RSUP Dr. M. Djamil Padang. Most subjects (42.06%) were less than 50 years old, half were female (56.15%), obesity was the most common comorbidity (41.39%), and most patients had moderate disease severity (42.06%). Elevated IL-6 levels (>7 pg/mL) were found in 87.47% of subjects. SGOT levels of ≥32 IU/L (46.76%) and SGPT levels of ≥31 IU/L (41.39%) were found in less than half of the subjects.

The initial analysis was carried out by using Kolmogorov-Smirnov to test the normality of the data on IL-6, SGOT, and SGPT levels based on the clinical severity of the COVID-19 patient. The non-parametric Kruskal-Wallis statistical test was performed for further analysis because the data were not normally distributed.

Table 1. Characteristics of COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

| Variable | n | % |
|---|---|---|
| Gender | | |
| Female | 251 | 56.15 |
| Male | 196 | 43.85 |
| Age | | |
| <50 | 188 | 42.06 |
| 50-59 | 112 | 25.05 |
| 60-69 | 90 | 20.13 |
| ≥70 | 57 | 12.75 |
| Comorbid | | |
| Obesity | 185 | 41.39 |
| Hypertension | 55 | 12.30 |
| Diabetes Mellitus | 51 | 11.40 |
| Cardiovascular | 23 | 5.14 |
| Chronic Kidney | 17 | 3.80 |
| Disease | | |
| Chronic Pulmonary | 10 | 2.23 |
| Cerebrovascular | 21 | 4.69 |
| Clinical Degree | | |
| Mild | 24 | 5.37 |
| Moderate | 188 | 42.06 |
| Severe | 96 | 21.48 |
| Critically ill | 139 | 31.10 |
| IL-6 | | |
| <7 pg/mL | 56 | 12.53 |
| ≥7 pg/mL | 391 | 87.47 |
| SGOT | | |
| <32 IU/L | 238 | 53.24 |
| ≥32 IU/L | 209 | 46.76 |
| SGPT | | |
| <31 IU/L | 262 | 58.61 |
| ≥31 IU/L | 185 | 41.39 |

Note: IL-6=interleukin 6; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase

Table 2 shows that patients with critical clinical severity have a higher level of IL-6 (92.20 pg/mL) than patients with severe clinical (75.30 pg/mL), moderate clinical (17.10 pg/mL), and mild clinical (11.90 pg/mL). IL-6 levels differed significantly across severity groups ($P<0.05$).

Table 2. IL-6 Level Differences Based on Clinical Severity of COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

| Clinical Severity | IL-6 Levels [Median (Min-Max)] | P |
|---|---|---|
| Mild | 11.90 (3.50 – 272.70) | 0.0001* |
| Moderate | 17.10 (1.05 – 3617.00) | |
| Severe | 75.30 (2.49 – 3287.00) | |
| Critical | 92.20 (1.50 – 3287.00) | |

Note: *P<0.05 significant with Kruskal-Wallis test

Table 3 shows that SGOT levels are higher at critical and severe clinical severity (39.00 IU/L) than at moderate (24.00 IU/L) and mild (21.00 IU/L). The findings revealed a significant difference in SGOT levels based on the clinical severity of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (P<0.05). SGPT level in critical clinical cases was higher (31.0 IU/L) than in severe clinical cases (28.50 IU/L), but mild clinical levels were higher (22.50 IU/L) than moderate clinical (20.00 IU/L). SGPT levels also showed significant differences across clinical severity levels (P<0.05).

Table 3. Differences in Liver Enzyme Levels Based on Clinical Severity of COVID-19 Patients Treated at RSUP DR. M Djamil Padang

| Clinical Severity | SGOT[a] | P | SGPT[a] | P |
|---|---|---|---|---|
| Mild | 21.50 (13-49) | 0.0001* | 22.50 (8-95) | 0.0001* |
| Moderate | 24.00 (7-220) | | 20.50 (5-213) | |
| Severe | 39.00 (11-439) | | 28.50 (3-402) | |
| Critical | 39.00 (5-3103) | | 31.00 (6-1753) | |

Note: *P<0.05 significant with Kruskal-Wallis test; [a]Median (Min-Max); IL-6=interleukin 6; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase

## DISCUSSION

According to the study's findings, women were treated more frequently than men (56.15% versus 43.8 %). The higher number of female cases may reflect regional COVID-19 distribution in West Sumatra, where females outnumber males 54.2% to 45.1%.[12] The findings of this study are similar to those of Mardewi's study in Bali, where women is more women than men (53.9% vs. 46.1%).[13] In Liu et al's study of 69 severe cases of COVID-19, there were 52.17% more women than men.[14] Kuehn's study also found a higher prevalence of COVID-19 in women (70%), but a higher death rate from COVID-19 in men.[15]

Another study, conducted in Germany by Doerre et al, reported that the incidence of COVID-19 was higher in working-age women. Higher contact rates may explain the greater number of female COVID-19 cases. Doerre's contact matrices research discovered a pattern in which women have a higher presentation of contact with COVID-19 cases (13-26%), but as age increases, especially in the 50-69 year range, men have a 9%-14% higher contact presentation. Due to a greater number of contacts, young and middle-aged women contribute to an increase in the incidence of infection.[16]

The findings of this study are inversely proportional to those of a study conducted in Ontario, Canada, which found that COVID-19 events were more common in men. These differences may be due to gender roles, behavior, and

occupational exposure that put men at a higher risk of COVID-19 infection. Men are more likely to work in fields that require them to work outside the home and interact with a large number of people. Furthermore, men are more likely to engage in risky behaviors such as smoking and drinking alcohol. Smoking is associated with higher ACE2 expression in type 2 pneumocytes and alveolar macrophages, resulting in a higher prevalence of COVID-19 in this subgroup.[17]

Women are thought to be less susceptible to COVID-19 than men due to differences in innate immunity, steroid hormones, and sex chromosomal factors. When compared to men, the immune regulatory gene encoded by the X chromosome in women causes inflammation and lower viral loads. T cells and TLR7 were found to be higher in women who had a better immune response.[18]

The majority of patients in this study were 18-49 years old (42.06%), followed by 50-59 years (25.05%), 60-69 years (20.13%) and 70 years (12.75%). The findings of this study are based on the discovery that people under the age of 50 have a twofold higher likelihood of close contact with COVID-19 cases. According to the Centers for Disease Control (CDC), social interaction, workplaces, and community transmission all play a role in the sharp increase in COVID-19 cases among young adults. Individuals aged 18–29 are more vulnerable due to lower adherence to handwashing, mask use, and social distancing.[19]

The findings of this study are consistent with research conducted by Malmgren et al in Washington in 2021, which discovered that the young adult age group (20-39 years) has the highest incidence of COVID-19. COVID-19 incidence decreased in the older age group and increased in the 20-39 year age group after the peak (March 22, 2020), rising from 20% to 40% of total cases.[19] Another study conducted by Yu in South Korea in 2020 found that the age group 20-39 years had the highest incidence of COVID-19 (37%), followed by the age group 40-59 years (31%).[20]

In contrast to the findings of this study, Dhama et al found that the elderly, particularly those with comorbidities, are more vulnerable to COVID-19. Preliminary COVID-19 studies revealed that there were more cases in the 49-55-year-old age group, indicating that the elderly, particularly those with comorbidities, are more vulnerable to COVID-19.[21]

Preliminary COVID-19 research found that the 49-55 age group had the highest number of cases. Subsequent studies with a larger sample size revealed that the prevalence of COVID-19 is higher in people over 60 than in younger people. Specific risk factors for the geriatric population include age-related decline in the physiological function of various organs, including the respiratory system, and impaired mucociliary clearance of foreign particles or microorganisms. Furthermore, aging has been linked to a

decline in the physiological functions of various vital organs as well as innate and adaptive immune defenses.[21]

The majority of patients (87.47%) had IL-6 levels of ≥7 pg/ml. Interleukin-6 is a cytokine that appears during the early stages of infection, particularly in the mucosa.[22] The biological effects of IL-6 production have been linked to both pro- and anti-inflammatory effects, emphasizing IL-6's importance in the activation and regulation of immune responses. Controlling monocyte differentiation into macrophages by regulating macrophage colony-stimulating factor, increasing B-cell IgG by regulating IL-21 expression, negative regulation of dendritic cell maturation through activation of the STAT3 signaling pathway, and enhancing Th2 response by inhibiting Th1 polarization are all biological activities influenced by IL-6 production.[22,23]

The combination of IL-6 and transforming growth factor beta induces the differentiation of naive CD4 cells into Th17 cells, which play an important role in mucosal defense against pathogens. The synergistic interaction of IL-6, IL-7, and IL-15 can also induce CD8 T cell differentiation. The effect of viruses on the body is to make the adaptive immune system release interferon; however, in the case of the SARS-CoV-2 infection, interferon release is delayed. This delay causes the viral load to rise, resulting in the uncontrolled release of inflammatory cytokines like IL-6. This overexpression can result in tissue damage to infected organs and worsen clinical outcomes.[22,23]

The findings of this study are comparable to those of Ananda et al in Palembang, who divided patients into two groups based on IL-6 levels, normal and high. This study discovered that only 16.1% of COVID-19 patients had normal IL-6 levels, while the majority (83.9%) had high IL-6 levels (100 pg/ml).[24] Another study, conducted in 140 COVID-19 patients by Liu et al, discovered that 67.9% of patients had IL-6 levels greater than 7 pg/mL.[4]

Liver enzymes showed an increase in SGOT (>32 IU/L) in 46.76% of patients and an increase in SGPT (>31 IU/L) in 41.39% of patients in this study. Several mechanisms have been proposed to explain the pathobiology of COVID-19 liver injury. The SARS-CoV-2 virus can bind to ACE2 on cholangiocytes, resulting in a systemic inflammatory response and liver damage. Other mechanisms that can cause hepatocyte injury include cytokine storms caused by hyperinflammation and metabolic disturbances caused by hypoxia.[25]

Other research suggests that several etiologies, including direct hepatic injury, inflammatory response, congestive hepatopathy, hepatic ischemia, drug-induced liver injury (DILI), and muscle damage, may contribute to elevated liver enzymes in SARS-CoV-2 patients. The findings of this study are similar to those of Hwaiz et al, who found that 40% of COVID-19 patients had elevated SGOT levels and 34.7% had elevated SGPT levels.[25] Another study, conducted in 2022 in India by Harisha et al, discovered higher

incidences of SGOT and SGPT, at 40.2% and 65.5%, respectively.[26]

The three most common comorbidities in this study were obesity (41.39%), hypertension (12.30%), and diabetes mellitus (11.40%). The findings of this study are consistent with the demographic information provided by the CDC for COVID-19 patients. The study, which included 180 COVID-19 patients who were hospitalized, discovered that 89.3% of them had comorbidities, with obesity, hypertension, and diabetes mellitus being the most common.[27] The findings of this study are also supported by reports from two Spanish hospitals' intensive care units, which identified obesity as the most common co-morbidity, accounting for 48% of all cases.[28]

Obesity has four mechanisms that increase the risk of SARS-CoV-2 infection and place patients in a severe clinical stage. First, because it increases ACE-2 expression, adipose tissue can serve as a reservoir for virus production, allowing SARS-CoV-2 to enter cells. Second, obesity is associated with impaired immune function, which prevents viral replication. Third, obesity increases inflammation, which affects the lung parenchyma and bronchi. Fourth, obesity can reduce lung capacity and reserves, making ventilation more difficult.[29]

In contrast to the findings of this study, Karyono et al in Indonesia reported in 2020 that hypertension (52.1%), diabetes mellitus (33.6%), and cardiovascular disease (20.9%) were the three most common comorbidities among confirmed COVID-19 patients. The most common cause of COVID-19 infection has been identified as hypertension. People with high blood pressure, according to the theory, have more RAAS inhibitors like ACE-2, which are linked to an increased susceptibility to COVID-19.[30] Diabetes and COVID-19 may be caused by SARS-CoV-2-induced chronic inflammation, increased coagulation activity, a weakened immune response, or direct pancreatic damage. Diabetes makes people more susceptible to bacterial, fungal, parasitic, and viral infections.[31]

In this study, the most severe clinical severity of COVID-19 was found to be moderate (42.06%), followed by critical (31.10%). The findings of this study are consistent with the characteristics of patients found in a study conducted by Liu in Beijing in 2020, which discovered that the majority of patients (49.53%) had moderate degrees, followed by critical degrees (23.08%).[32] This study's findings differ from those of Li et al in Wuhan, China, who reported that 49.1% of patients in the severe category were treated at Tongji Hospital from January 26 to February 5, 2020. This disparity in findings could be attributed to the fact that Wuhan experienced its highest peak of the COVID-19 outbreak from mid-January to early February, with familial clusters and a high prevalence of COVID-19 in older adults.[33]

The prevalence of mild clinical symptoms in COVID-19 patients was found to be 5.4% in this study. According to the COVID-19 management guidelines,

COVID-19 patients with mild clinical symptoms receive outpatient treatment followed by independent isolation, but patients with mild COVID-19 require hospitalization if comorbidities or coincidences exist.[2]

According to the findings of this study, IL-6 levels were higher in patients with critical clinical conditions than in patients with severe, moderate, and mild conditions. There is a significant difference in IL-6 levels between COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang, based on clinical severity. The higher the clinical severity, the higher the IL-6 level tends to be.

Monocytes and macrophages produce IL-6 in the early stages of infection. Interleukin 6 plays a critical role in the cytokine storm in COVID-19. Interleukin-6 is a pro-inflammatory molecule that can activate inflammatory cells and other mediators in the lungs, causing parenchymal damage and dyspnea. High levels of IL-6 prevent NK cells from releasing perforin and granzyme B, preventing infected cells from dying and resulting in continuous antigen stimulation. Increased IL-6 levels are followed by an increase in immune cell proliferation, which causes the release of proinflammatory cytokines and chemokines. This is referred to as a "cytokine storm." A cytokine storm causes lung damage, which leads to ARDS and multi-organ dysfunction.[34]

Coome et al discovered that serum IL-6 levels were significantly higher in patients with severe COVID-19 in a meta-analysis study.[35] According to available data, elevated levels are significantly associated with negative outcomes such as intensive care, ARDS, and death. Serum IL-6 levels in these COVID-19 patients were nearly three times higher than in those without complications. According to Chen et al, a cut-off value of 55 pg/mL could indicate a severe course of the disease, whereas in other studies, a cut-off value of 80 pg/mL could indicate mortality.[36]

A retrospective analysis of IL-6 levels in serum samples of 68 infected patients conducted by Sun et al in 2020 discovered that IL-6 levels were significantly higher in patients with severe COVID-19 symptoms than mild symptoms, and that of the 40 seriously ill patients, 8 developed a critical degree of COVID-19 and experienced respiratory failure. Interleukin-6 levels were significantly higher in these eight patients than in 32 other critically ill patients, with IL-6 levels in one patient increasing up to 23 times after developing a critical illness.[37] These findings were nearly identical to those found in this study, where the highest IL-6 value was found in one patient in the critical clinical degree group, with an IL-6 value of 3287 pg/mL.

This study also discovered that 70.8% of mild clinical COVID-19 patients had an increase in IL-6 7 pg/mL, with the highest IL-6 level being 272.70 pg/mL. In the study by Gao et al, IL-6 levels in mild clinical COVID-19 were also elevated. Age, gender, the immune system, and

comorbidities are all factors that influence these conditions.[38]

Sun et al's study confirmed that IL-6 is closely related to infection severity, but it also demonstrated that IL-6 plays an important role in the occurrence of COVID-19 lung injury. Interleukin-6 can rapidly activate pathogenic T cells during COVID-19 infection, causing them to produce GM-CSF, IL-6, and other factors. GM-CSF then activates CD14+ and CD16+ inflammatory monocytes, increases IL-6 production, and initiates a positive feedback loop, causing diffuse damage to alveolar and pulmonary capillary endothelial cells. Large amounts of exudate can clog the airways, resulting in pneumonia and ARDS.[37]

This study reported that SGOT and SGPT levels differed depending on the clinical severity of COVID-19 patients. There is a trend toward higher SGOT and SGPT levels as clinical severity rises. In this study, SGOT levels were 39.00 IU/L and SGPT levels were 31.00 IU/L in the clinically critical group. In mild- moderate cases, the majority of patients with clinically critical degrees had increased SGOT, namely 60.4% and 51.1% of 139 patients, respectively, whereas only a few patients had abnormal SGOT and SGPT values.

The following hypotheses explain the mechanism of COVID-19-induced liver injury: First, the replication of the SARS-CoV-2 virus in the liver causes direct cytotoxicity.[11,43] SARS-CoV-2 RNA is found in stool and blood samples, proving hepatic exposure to the virus in approximately 2-10% of COVID-19 patients.[10] Although ACE2 expression was higher in cholangiocyte cells, increases in gamma-glutamyl transferase and alkaline phosphatase as biomarkers of cholangiocyte cell injury have been reported in a few studies.[39]

The second is immune-mediated liver damage as a result of COVID-19's systemic inflammatory response syndrome (SIRS), hypoxia as a result of respiratory failure, vascular changes as a result of coagulopathy, or endothelial or cardiac congestion as a result of right heart failure.[40] Ponziani et al discovered a link between abnormal liver function tests and IL-6 levels, demonstrating that liver injury is a result of systemic inflammation in COVID-19.[11]

According to this study, there is a trend toward higher IL-6, SGOT, and SGPT levels as the clinical stage of COVID-19 patients advances. McConnel et al described the relationship between IL-6 and liver injury as follows: an increase in IL-6 causes IL-6 signaling in the liver sinusoidal endothelial cell (LSEC) via the Janus kinase (JAK) or the signal transducer and activator of transcription (STAT), resulting in an increase in pro-coagulant and pro-inflammatory genes, which activate the thrombosis pathway and cause hypercoagulopathy. Hypercoagulopathy results in vascular changes that can harm hepatocyte cells.[9]

According to the findings of various studies, there is a correlation between the severity of COVID-19 and the degree of liver dysfunction. The findings of this study are consistent with those of Hwaiz et al,

who discovered that the majority of patients with abnormal liver enzyme levels received a course of COVID-19 with more severe signs and symptoms (31 out of 48 cases).[25] Patients with a severe case of COVID-19 have more liver dysfunction.[39]

According to Huang et al, 62% of the 13 patients treated in the intensive care unit had an increase in AST, compared to 25% of the 28 patients treated in the usual room.[41] According to reports, COVID-19 clinical severity and advanced age predispose to more severe liver damage. This necessitates more stringent clinical monitoring and consideration when administering therapy to certain individuals who are at risk of liver injury.[42]

In COVID-19 patients, the prevalence of elevated hepatic enzyme levels ranges from 2.5% to 76.3%.[40] Boregowda et al found that patients with severe COVID-19 had significantly higher liver enzyme levels than patients with mild COVID-19 in a meta-analysis study. A pooled analysis also revealed that the non-survival group had significantly higher serum hepatic enzyme activity than the surviving group.[43]

Higuera et al reported an increase in hepatic enzyme levels of 16-62% in COVID-19 patients in another study. Patients with severe COVID-19 have abnormal liver enzyme levels.[44] According to one study, 52% of patients who died had elevated SGOT levels, with an average serum concentration of 45 UI/L.[45]

In their study, Lei et al discovered that in COVID-19, there was an increase in SGOT levels first, followed by an increase in SGPT levels.[46] Previous research has also found that in severe clinical situations, SGOT increases more frequently than SGPT.[41] Because SGOT enzymes can be found in disorders of other organs such as the heart, skeletal muscles, kidneys, brain, pancreas, and white and red blood cells, they are not specific for liver injury.[47]

An increase in SGOT correlates with an increase in neutrophils and a decrease in lymphocytes in COVID-19, according to ordinal regression analysis. This finding implies that immune-mediated inflammation may play a significant role in the development of liver injury in clinically severe COVID-19 patients. More research is needed to determine the mechanism underlying the increase in initial AST in COVID-19 patients.[46]

COVID-19 patients in this study were found to have comorbidities such as hypertension, cardiovascular disease, chronic kidney disease, chronic lung disease, and cerebrovascular disease. More research is needed to determine whether other extrahepatic conditions, such as cardiovascular disease, also cause the increase in SGOT and SGPT. This is one of the study's limitations. This study also has limitations, such as the fact that it is a retrospective study based on data collected from patient medical records and that the distribution of patients in this study at different clinical levels is uneven.

## CONCLUSION

Significant differences exist in IL-6, SGOT, and SGPT levels based on COVID-19

clinical severity. IL-6, SGOT, and SGPT levels were higher in critically ill patients than in those with milder illnesses.

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Original Article

# The Correlation between Air Pollution Levels in East Jakarta and COPD Exacerbation at Persahabatan Hospital in 2019

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## Abstract

**Background:** Air pollution has become a global environmental issue that has an impact on public health. Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that can be caused by exposure to noxious gases and environmental factors. Cigarette smoke is a major risk factor for the development of COPD. However, several studies have shown that environmental exposures such as air pollution can contribute to the worsening of COPD. This study aimed to evaluate the correlation between the level of air pollution and exacerbation of COPD in East Jakarta in 2019.

**Method:** This was a retrospective cohort study on COPD patients who experienced exacerbation in 2019 and came to the emergency room of Persahabatan National Respiratory Referral Hospital (PNRRH). Data was taken from the medical records by consecutive sampling. Data on the Index of Air Pollution Standards were obtained from the DKI Jakarta Provincial Environmental Service.

**Results:** A total of 198 subjects met the inclusion criteria. Most of the subjects were male (92.4%), and the mean age was 63.39 years. Three pollutants had a positive correlation with COPD exacerbation rates, including $PM_{10}$ (r=0.245), $SO_2$ (r=0.497), and $O_3$ (r=0.344). While the negative correlation were the levels of CO (r=-0.187) and $NO_2$ (r=-0.366). However, the correlations were not statistically significant.

**Conclusion:** $PM_{10}$, $SO_2$, and $O_3$ are correlated with COPD exacerbations, whose visits to the emergency department of Persahabatan hospital. However, this correlation does not establish a cause-and-effect correlation because there are still other factors that trigger COPD exacerbations.

**Keywords:** air pollution, COPD exacerbations, East Jakarta

## INTRODUCTION

Air pollution has become a global environmental issue with significant impacts on public health, especially on the respiratory system. Air pollution is one of the risk factors for the occurrence of Chronic Obstructive Pulmonary Disease (COPD).[1,2] Several studies have shown that exposure to environmental air pollution is a key determinant in the development of

COPD.[2,3] However, there are other significant factors involved in the development of COPD, such as genetic factors and abnormalities in lung development.[4]

Recent studies have indicated a correlation between exposure to air pollutants, such as particulate matter (PM), and the occurrence of COPD exacerbations.[3] Studies conducted in the United States and Europe have concluded that for every 10 µg/m³ increase in $PM_{10}$ levels, there is a 2.5% increase in the number of hospital visits due to COPD. Similarly, for every 10 µg/m³ increase in $PM_{2.5}$ levels, there is a 0.9% increased risk of hospitalization due to COPD. Additionally, a 5 ppb (parts per billion) increase in ozone ($O_3$) levels leads to a 0.27% increase in hospital admissions due to COPD exacerbations.[5]

Every 1 mg/m³ increase in CO gas levels is associated with an increased need for hospitalization due to COPD.[6] Currently, no research directly links air pollutant exposure to COPD exacerbations in Indonesia. This study aimed to investigate the correlation between air pollutant levels in East Jakarta and the incidence of acute COPD exacerbations among patients who presented at the Emergency Department of Persahabatan National Respiratory Referral Hospital (PNRRH) in 2019.

## METHOD

This research employed a retrospective cohort design. Sample collection was conducted through consecutive sampling, and data from subjects meeting the inclusion criteria were extracted from medical records. The subjects in this study were patients diagnosed with COPD exacerbation who were above 40 years old and resided in East Jakarta, who visited the Emergency Department of PNRRH during the period from January 1, 2019, to December 31, 2019.

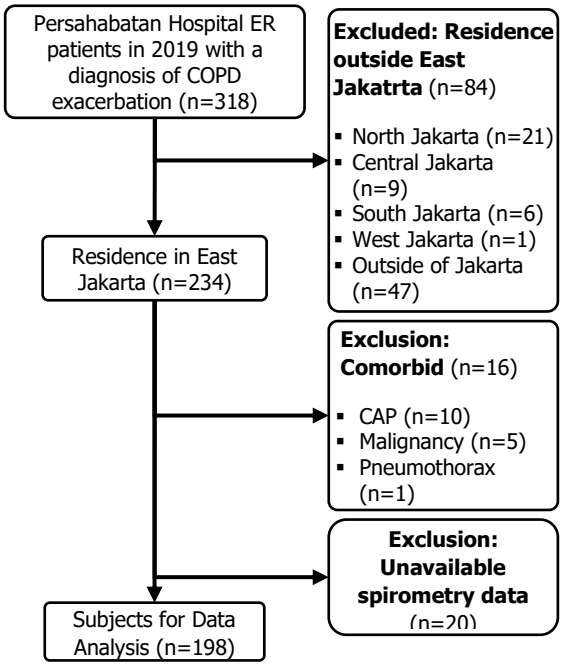


Figure 1. Flow of subject recruitment

Patients with COPD who had comorbidities such as cancer, pneumonia, asthma, and pneumothorax were excluded from this study. Data on the standard air pollution index (ISPU) in East Jakarta for the year 2019 was obtained from the Environmental Agency of DKI Jakarta Province, which includes particulate matter ($PM_{10}$), sulphur dioxide ($SO_2$), carbon monoxide (CO), ozone ($O_3$), and nitrogen dioxide ($NO_2$).

The research data in this study were processed using the statistical program

SPSS for Windows version 22.0. The correlation between air pollutant levels and the incidence of COPD exacerbation was analyzed using the Pearson correlation coefficient when data distribution was normal or the Spearman correlation if the data distribution was not normal.

## RESULT

In this study, 198 COPD exacerbation patients met the inclusion criteria. The mean age was 63.39±9.11 years, with the majority of subjects being male (92.4%).

Table 1. Demographic characteristics

| Characteristic | n (%) |
|---|---|
| Age (mean±SD) | 63.39±9.11 |
| 41-65 Years | 118 (59.6%) |
| ≥66 Years | 80 (40.4%) |
| Sex | |
| Male | 183 (92.4%) |
| Female | 15 (7.6%) |
| ER visitation period | |
| January | 17 (8.6%) |
| February | 15 (7.6%) |
| March | 12 (6.1%) |
| April | 16 (8.1%) |
| May | 15 (7.6%) |
| June | 17 (8.6%) |
| July | 15 (7.6%) |
| August | 16 (8.1%) |
| September | 16 (8.1%) |
| October | 21 (10.6%) |
| November | 13 (6.6%) |
| December | 25 (12.6%) |
| Body Mass Index (mean±SD) | 21.52±3.7 |
| Normal | 119 (60.1%) |
| Underweight | 28 (14.1%) |
| Risk | 18 (9.1%) |
| Type 1 Obesity | 28 (14.1%) |
| Type 2 Obesity | 5 (2.5%) |
| Brinkman Index | |
| Non-Smoker | 15 (7.6%) |
| Mild BI | 5 (2.5%) |
| Moderate BI | 29 (14.6%) |
| Severe BI | 149 (75.3%) |
| Distance to SPKU (mean±SD) | 9.7±1.5 |
| 0.0-10.0 km | 137 (69.2%) |
| 10.1-15.0 km | 61 (30.8%) |

Most of the subjects were smokers, with 75.3% of them having a heavy smoking history. The mean distance from the subjects' residence to the Air Quality Monitoring Station, or *Stasiun Pemantau Kualitas Udara* (SPKU), was 9.7 km. A total of 119 subjects had a normal BMI. The highest number of emergency department visits due to COPD exacerbation was in December, with a total of 25 (12.6%) visits (Table 1). The majority of patients belonged to the COPD group E (94.4%) and the exacerbation group without respiratory failure (77.3%) (Table 2).

Table 2. Clinical characteristics of study subject (n=198)

| Characteristic | n (%) |
|---|---|
| Treatment category | |
| Outpatient | 105 (53.0%) |
| Inpatient | 93 (47.0%) |
| Length of inpatient stay (Days) [Median (Min-Max)] | 4 (1-24) |
| COPD Group | |
| Group A | 1 (0.5%) |
| Group B | 10 (5.1%) |
| Group E | 187 (94.4%) |
| GOLD Criteria | |
| GOLD 1 | 12 (6.1%) |
| GOLD 2 | 43 (21.7%) |
| GOLD 3 | 84 (42.4%) |
| GOLD 4 | 59 (29.8%) |
| COPD Exacerbation Category | |
| Without respiratory failure | 153 (77.3%) |
| Respiratory failure without a life-threatening condition | 29 (14.6%) |
| Respiratory failure with a life-threatening condition | 16 (8.1%) |

The Standard Air Pollution Index or *Indeks Standard Pencemar Udara* (ISPU) is divided into five categories: good (0-50), moderate (51-100), unhealthy (101-199), very unhealthy (200-299), and hazardous (≥300).

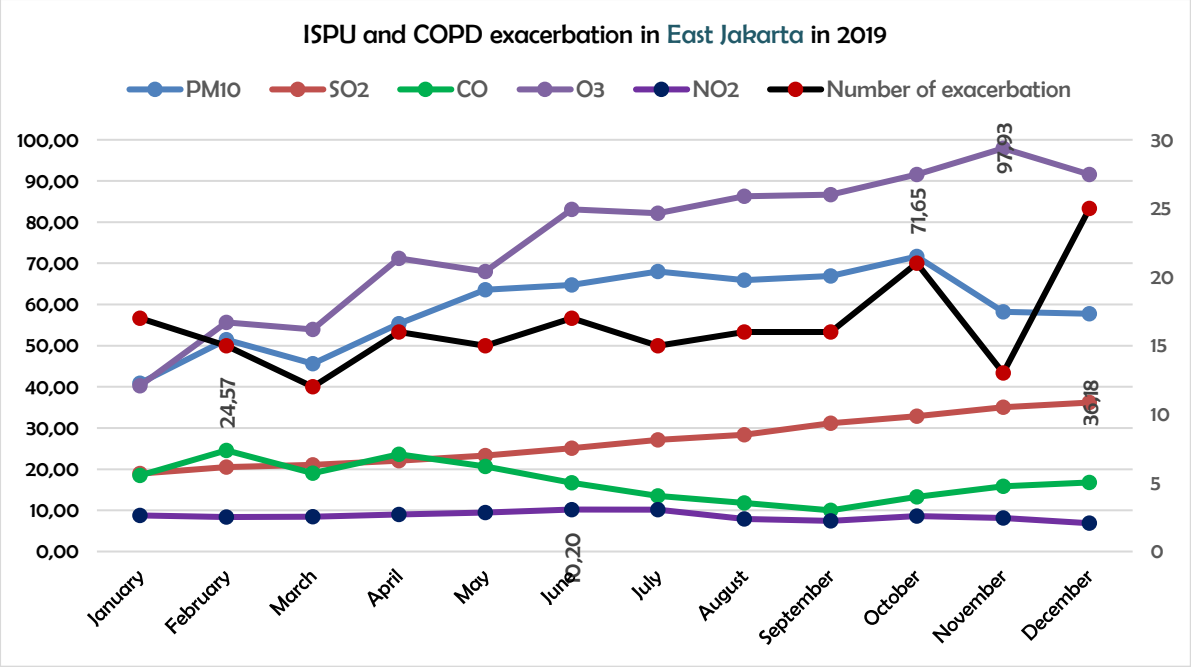


Figure 2. Air pollutant levels and number of COPD exacerbations in East Jakarta in 2019

For the East Jakarta region, $PM_{10}$ and $O_3$ levels reached moderate levels, while $SO_2$, CO, and $NO_2$ were still within good air pollution index standards. The highest $PM_{10}$ levels were recorded in October, while the highest levels of $SO_2$, CO, $O_3$, and $NO_2$ were observed in December, February, November, and June, respectively (Figure 2).

Among the five air pollutants, $O_3$ and $PM_{10}$ had the highest ISPU levels and fell into the 'moderate' category. Meanwhile, the ISPU levels for $SO_2$, CO, and $NO_2$ remained in the 'good' category. The lowest ISPU level was attributed to $NO_2$. The ISPU levels, such as $PM_{10}$, $SO_2$, and $O_3$, showed a positive correlation with the number of COPD exacerbations, but the correlation was weak. Meanwhile, the correlation between CO and $NO_2$ levels and COPD exacerbations demonstrated a negative correlation with a very weak strength.

Table 3. Mean air pollution levels at the time of COPD exacerbation

| Air Pollution exposure | Mean±SD) or Median (Min-Max) |
|---|---|
| $PM_{10}$ | |
| $PM_{10}$ D-day | 60.50 (17-90) |
| $PM_{10}$ D-3 | 59.81±11.70 |
| $PM_{10}$ D-7 | 59.48±10.46 |
| $PM_{10}$ Monthly | 59.52±9.00 |
| $SO_2$ | |
| $SO_2$ D-day | 28.00 (7-37) |
| $SO_2$ D-3 | 27.33 (7-43) |
| $SO_2$ D-7 | 27.29 (9.43-37.29) |
| $SO_2$ Monthly | 27.13 (18.93-36.18) |
| CO | |
| CO D-day | 16.00 (5-46) |
| CO D-3 | 16.50 (5.33-39.67) |
| CO D-7 | 16.65 (6.29-78.79) |
| CO Monthly | 16.76 (10-24.57) |
| $O_3$ | |
| $O_3$ D-Day | 75.00 (13-185) |
| $O_3$ D-3 | 79.84 (17.67-143.0) |
| $O_3$ D-7 | 78.65 (26.86-130.64) |
| $O_3$ Monthly | 83.10 (40.27-97.93) |
| $NO_2$ | |
| $NO_2$ D-Day | 8.00 (3-19) |
| $NO_2$ D-3 | 8.67 (3.67-16) |
| $NO_2$ D-7 | 8.71±1.71 |
| $NO_2$ Monthly | 8.55±1.01 |

Table 4. Correlation of particulate matter with COPD exacerbation

| Particulate Matter | COPD Exacerbation | |
|---|---|---|
| | r | *P* |
| $PM_{10}$ | 0.26 | 0.44 |
| $SO_2$ | 0.50 | 0.10 |
| CO | - 0.19 | 0.56 |
| $O_3$ | 0.34 | 0.27 |
| $NO_2$ | - 0.37 | 0.24 |

## DISCUSSION

$PM_{10}$ has a significant correlation with COPD exacerbations.[7–9] In this study, a positive correlation is observed between $PM_{10}$ levels and the incidence of COPD exacerbations. Patients experiencing COPD exacerbations are exposed to an average $PM_{10}$ ISPU value of 59.52±9.00, which is equivalent to a $PM_{10}$ concentration of 150 µg/m$^3$. The COPD exacerbations correlate with $PM_{10}$ on the day of exacerbation (ISPU 60.5), in the last 3 days (59.81), the last 7 days (59.48), and the monthly $PM_{10}$ level (59.52).

Morantes-Caballero and colleagues found an increase in $PM_{10}$ levels two days before the onset of COPD exacerbation symptoms.[7] The study by Krachunov et al also found a significant correlation between the average $PM_{10}$ levels in the six days preceding COPD exacerbation.[8] Research in New Zealand yielded results indicating that each 14.8-unit increase in $PM_{10}$ leads to a 3.37% increase in the incidence of COPD exacerbations.[9]

A systematic review and meta-analysis concluded that there is a correlation between short-term exposure to $PM_{10}$ and the risk of COPD exacerbations.[9] The most significant correlation between COPD exacerbations and $PM_{10}$ levels is observed in the three days leading up to the exacerbation.[10]

Several previous studies have demonstrated a positive correlation between $SO_2$ levels and the incidence of COPD exacerbations.[9,11–13] In this study, a positive correlation is found between $SO_2$ levels and the incidence of COPD exacerbations. Patients experiencing COPD exacerbations are exposed to an ISPU $SO_2$ value of 27.13 (18.93-36.18), which is equivalent to 52 µg/m$^3$. This value exceeds the threshold recommended by the World Health Organization (WHO), which is 20 µg/m$^3$.

A systematic review conducted by Moore and colleagues stated differing results between geographical regions. In the Asian region, there is a stronger positive correlation compared to Europe and North America. The average $SO_2$ levels in Asia are also higher than in Europe and North America, with levels of 25.1±11.3, 18±3.2, and 18.1±4.7 µg/m$^3$, respectively. Additionally, research in Taiwan found that the correlation between $SO_2$ levels and COPD exacerbations only occurred during the winter season.[14]

The study of the correlation between CO and COPD exacerbation were inconsistent. In this study, we obtained a negative correlation between CO levels and the incidence of COPD exacerbations with a correlation coefficient of r=-0.187 (P=0.561). Patients experiencing COPD exacerbations are exposed to an ISPU CO value of 16.76 (10-24.57), equivalent to 4000 µg/m$^3$. The results of this study are in line with findings from research in

Shanghai and Hong Kong, where they also observed a negative correlation between short-term CO exposure and the incidence of COPD exacerbations and hospitalizations. This negative correlation is more pronounced during the winter season.[15,16]

One hypothesis proposed is that COPD is an inflammatory disease, and the anti-inflammatory effects of exogenous CO have been suggested in some experimental and clinical trials. The first human pilot study on the impact of CO on COPD indicated that inhalation of CO at concentrations of 100-125 ppm by COPD patients resulted in a reduction in eosinophil counts in sputum and an increase in response to methacholine. Additionally, several reviews in the literature suggest that exogenously administered CO through CO-releasing molecules can have antimicrobial effects.[15,16]

There is a positive correlation between $O_3$ levels and COPD exacerbations. Patients with COPD exacerbations are exposed to an ISPU $O_3$ value of 83.1 (40.27-97.93), which is equivalent to 235 µg/m$^3$. Studies by Gao et al and Sun et al show a stronger correlation between $O_3$ exposure and COPD exacerbations during the summer and winter. This can be attributed to higher $O_3$ concentrations during the summer and increased outdoor activities, leading to greater exposure to air pollution, including $O_3$.[17] Conversely, Lin et al found that during the summer, with higher $O_3$ levels, lower exacerbation rates were observed. During the winter, with lower $O_3$ levels resulting in higher exacerbation rates.[18]

In this study, a negative correlation is observed between $NO_2$ levels and the incidence of COPD exacerbations. Patients experiencing COPD exacerbations are exposed to an average ISPU $NO_2$ value of 8.55±1.01, equivalent to 80 µg/m$^3$. This finding differs from the positive correlation observed in the study by Lin et al, with a correlation coefficient of r=0.763 (P<0.05). Research in Taiwan found a correlation between increased $NO_2$ levels and the incidence of COPD exacerbations during both the summer and winter seasons. Every one ppb increase in $NO_2$ was associated with a 1.00-1.30 odds ratio for COPD exacerbations.[18]

Other studies have reported an increase in visits to the emergency department and hospitalizations due to COPD exacerbations associated with higher $NO_2$ concentrations.[13,19] It has also been stated that each 10 µg/m$^3$ increase in $NO_2$ levels increases the incidence of COPD exacerbations by 2%.[13] Meta-analysis studies have found an increase in the number of COPD exacerbations with rising environmental $NO_2$ levels. This is more pronounced in low- and middle-income countries.[9] Similar results were obtained in the study by Du et al, which concluded that a 10 µg/m$^3$ increase in $NO_2$ levels is related to the incidence of COPD exacerbations.[20]

There are several limitations in this study. Firstly, this study was conducted retrospectively, so data quality depends on the completeness of medical records. Second, the subjects of the study were only

obtained from one hospital in East Jakarta and air pollution data were gathered only from one SPKU point. Third, there were variations in the distance of the subject's house/residence from SPKU, which could potentially cause variation in the amount of air pollution exposure among subjects.

Apart from that, several factors can affect air pollution levels in the environment, such as air temperature and wind direction/speed. Fourth, the level of air pollution used is ISPU, which is different from the literature abroad, who generally use units of $\mu g/m^3$. Lastly, there is no data comparison with the stable COPD group or healthy subjects.

## CONCLUSION

Air pollution levels in East Jakarta have exceeded the established thresholds, resulting in an influence on COPD exacerbations. $PM_{10}$, $SO_2$, and ozone are particles from air pollution that are correlated with COPD exacerbations and visits to the emergency department of Persahabatan Hospital. The association between pollutant exposure and the occurrence of COPD exacerbations varies from findings in other studies. These disparities may be due to differences in research designs, variations in demographic profiles between countries/regions, fluctuations in local air temperatures and climates, disparities in other air pollutant concentrations, and other factors. Moreover, it is essential to note that this study was conducted solely at a single hospital in East Jakarta, utilizing air quality data from a solitary air quality monitoring station.

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Original Article

# Positivity Rates of Histology Results Based on Lesion Size and Bronchus Sign in Lung Cancer

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## Abstract

**Background:** Lung cancer continues to be a major cause of cancer-related deaths globally. Bronchoscopy serves as a key diagnostic tool, allowing histological sampling through transbronchial biopsy (TBB). The bronchus sign, identified on pre-biopsy CT scans, is associated with improved diagnostic yield in TBB.

**Method:** A retrospective study was conducted between October and December 2023 at Persahabatan Hospital, Jakarta, analyzing 88 patients suspected of lung cancer. Data collected comprised patient demographics, lesion size as determined by CT scans, and the presence or absence of the bronchus sign. Fisher's exact test was applied for statistical analysis, with a predetermined significance level of $P<0.05$.

**Results:** Positive histology results were identified in 38 cases (55.07%) for lesions ≥3 cm and 9 cases (47.39%) for <3 cm($P=0.607$). In lesions ≥3 cm, the positivity rate was similar between those with the presence (55.81%) and absence (53.85%) of a bronchus sign ($P>0.99$). In lesions <3 cm, positivity was higher with a bronchus sign (60%) than without (25%) ($P=0.55$).

**Conclusion:** The bronchus sign appears to increase TBB positivity, especially in peripheral lesions <3 cm. Lesion size also appears to influence TBB yield. However, the findings were not statistically significant, likely due to small sample size and missing CT data.

**Keywords:** bronchoscopy, bronchus sign, lung cancer, transbronchial biopsy

## INTRODUCTION

Lung cancer remains a leading malignancy and cause of cancer-related deaths in Indonesia and worldwide. According to Global Cancer Statistics 2022, lung cancer was the most diagnosed cancer, with 2.5 million new cases, accounting for 12.4% of all newly reported cancers. It also remained the leading cause of cancer-related deaths, contributing to

1.8 million fatalities (18.7% of total cancer deaths).[1,2]

Early detection and surgery are key to improving survival, with a five-year survival rate of 66-82% in early-stage non-small cell lung cancer (NSCLC).[3,4] Imaging plays a key role in early detection, with chest X-rays identifying nodules as small as 0.5-1 cm, while CT scans provide clearer detail of lesion size and location.[5,6]

Bronchoscopy is a primary diagnostic tool for suspected lung cancer, enabling tissue sampling through transbronchial biopsy (TBB), transbronchial needle aspiration (TBNA), airway electrosurgery, or cryotherapy.[7] Factors affecting diagnostic yield include lesion size, location, and bronchus sign, which indicates whether a bronchus leads directly to the lesion on a pre-biopsy CT scan.[8]

The bronchus sign indicates the presence of bronchi within the target identified on the pre-biopsy thoracic CT scan.[9] However, if the bronchus sign remains unclear, it may be prudent to consider bronchoscopy with TBB as a diagnostic modality, as the positive yield is often low in the absence of additional diagnostic tools.[10] Several studies indicate that diagnostic outcomes are influenced by target lesion characteristics, including size, proximity to the hilum, and the bronchus sign.[11]

Tsuboi's classification categorizes tumor-bronchus relationships to guide TBB. Type I: patent bronchus leading to the tumor; Type II: bronchus within the tumor; Type III: compressed bronchus; Type IV: severely narrowed proximal bronchus.[12,13]

Since the Tsuboi classification cannot be fully applied to the relationship of the bronchi to peripheral lesions on CT, the subclassification of the CT-bronchus sign (CT-BS), which is more practical, is proposed. Ultimately, this classification was simplified into two categories: positive and negative CT-BS. This subclassification is highlighted as a practical and effective guiding method, as it enhances diagnostic success by enabling lesion access with minimal additional equipment, such as fluoroscopy.[11,14,15]

Transbronchial biopsy is a technique for sampling lung parenchyma using forceps through the distal tip of a flexible bronchoscope. TBB is recommended for suspected lung cancer, with a sensitivity of approximately 85% for endobronchial lesions, 60-70% for peripheral lesions, and 56% for nodules <20 mm.[3,16,17] Diagnostic yield for lesions <3 cm varies from 14-50%, compared to 46-80% for lesions ≥3 cm. Fluoroscopy improves TBB accuracy but requires expertise.[18,19]

Transbronchial biopsy samples can be acquired using various techniques, including fluoroscopy guidance, CT navigation, radial-probe endobronchial ultrasound, bronchial mapping, augmented fluoroscopy, cone beam-CT, robotic-assisted bronchoscopy, or electromagnetic navigation.[20,21] Diagnostic yield increases with more biopsy samples. Positive TBB results reach 70%, improving further with combined bronchial brushing and TBNA.[22,23]

Previous studies have shown that small peripheral pulmonary lesions (PPLs)

invisible under fluoroscopy can be accurately located using a three-dimensional localization technique on the chest wall surface, allowing bronchoscopy procedures to increase diagnostic yields.[24] Other factors influencing the diagnostic yield include lesion size, its proximity to the hilum (with higher yield observed in lesions closer to the hilum), visibility on fluoroscopy, malignancy status, and the combination of diagnostic tools used.

Meanwhile, determining whether a lesion is small or large is not the same between one study and another. Sanchez-Font et al, for example, used a cutoff of <30 mm, while Boonsarngsuk et al and Ishid et al used a cutoff of <20 mm.[25] Fluoroscopy in TBB for focus can improve diagnostic results by helping to determine the target area more accurately.[26]

## METHOD

This retrospective study was conducted from October to December 2023 at Persahabatan Central General Hospital, East Jakarta, using medical records. Ethical clearance was obtained before the study. All procedures were carried out in line with the ethical principles of the Declaration of Helsinki. After informed consent, fluoroscopy-guided TBB was performed on 88 patients with suspected peripheral lung cancer.

All patients underwent a Thoracic CT scan with contrast before image-guided bronchoscopy with fluoroscopy guidance. Bronchoscopic instruments included Olympus Exera 3 and Fujinon 7700. Anatomical pathology diagnosis was performed by a specialist at Persahabatan Hospital.

After localizing the lesion with fluoroscopy, forceps were inserted to reach the target. Once positioned, the forceps were opened and advanced into the lesion. A minimum of 4–5 specimens were obtained for analysis.

## RESULT

This study included 88 patients with suspected peripheral lung cancer at Persahabatan Hospital, East Jakarta, from October to December 2023. The study included 59 males and 29 females, with 71 participants aged ≥40 years and 17 <40 years. Bronchus signs were present in 53 CT scans, absent in 17, and missing in 18, which were excluded. The characteristics of the patients are presented in Table 1.

Table 1. Patient characteristics (n=88)

| Variable | n (%) |
|---|---|
| Age (mean) | |
| <40 | 17 (19.1%) |
| ≥ 40 | 71 (79.8%) |
| Gender | |
| Male | 59 (66.3%) |
| Female | 29 (32.6%) |
| Lesion size | |
| <3cm | 19 (21.3%) |
| ≥3cm | 69 (77.5%) |
| Bronchus Sign | |
| Presence | 53 (59.6%) |
| Absence | 17 (19.1%) |
| Exclude | 18 (20.2%) |

In this study, the pathology results were compared between two groups based on lesion size: ≥3 cm and <3 cm. Table 2 presents the distribution of histology

results for each group. Among lesions ≥3 cm, 38 cases (55.07%) were positive; in lesions <3 cm, 9 cases (47.39%) were positive.

Fisher's exact test was conducted to determine the significance of these discrepancies with results were not statistically significant (P=0.607), the odds ratio was found to be 1.39 with a 95% confidence interval (CI) of 0.53–3.77, indicating a tendency for higher odds of positive pathology results in the ≥3 cm group compared to the <3 cm group.

This study also evaluated the histology results between the two groups based on the presence and absence of bronchial indications. Table 2 presents the distribution of histology results in each group. In lesions ≥3 cm with a bronchus sign, 24 cases (55.81%) were positive, while in the group without a bronchial sign, 7 cases (53.85%) had a positive histological outcome.

Fisher's exact test was done to determine the significance of these differences, and the results show that the odds ratio was obtained at 1.083 with 95% CI=0.31-3.77), indicating no significant difference between groups with and without a bronchus sign, but this result is not statistically significant (P>0.99). The findings are further illustrated in Table 2, which visually represents the percentage of each tumor size group's positive histology findings.

In this study, histology results were compared between two groups based on the presence or absence of a bronchus sign in lesions <3 cm. Table 2 presents the distribution of pathology results in each group. In the group with the bronchus sign, six cases (60%) had positive histology results, while only 1 case (25%) was positive in the group without a bronchus sign.

Fisher's exact test was performed to determine the significance of these differences and the results was not statistically significant (P=0.55), the odds ratio was 4.5 with a 95% CI=0.45–66.62, which showed a tendency for a higher chance of positive histology results in the group with bronchus signs compared to the group without bronchus signs. Table 2 shows the proportion of positive histology results by bronchus sign in <3 cm lesions.

Table 2. Proportion of positive histology results based on lesion size, bronchus sign in group size ≥3cm, and Bronchus sign in group size <3cm

| Group | Positive | Negative | P | OR (95% CI) |
|---|---|---|---|---|
| Lesion size | | | | |
| <3cm | 9 (47.37%) | 10 (52.63%) | 0.607* | 1.39 (0.53–3.77) |
| ≥3cm | 38 (55.07%) | 31 (44.92%) | | |
| Bronchus sign in group size ≥3cm | | | | |
| Presence | 24 (55.81%) | 19 (44.19%) | >0.99 | 1.083 (0.31-3.77) |
| Absence | 7 (53.85%) | 6 (46.15%) | | |
| Bronchus sign in group size <3cm | | | | |
| Presence | 6 (60.00%) | 4 (40.00%) | 0.55 | 4.5 (0.45–66.62) |
| Absence | 1 (25.00%) | 3 (75.00%) | | |

Note: *Fisher's exact test with P>0.05 not significant; OR=odds ratio

## DISCUSSION

The study involved patients with suspected lung cancer at Persahabatan General Hospital, East Jakarta, from October to December 2023. The sample was 88 people, with patients >40 years old (79.8%). The majority of patients were males (66.3%) with a tumor size generally ≥3 cm (77.5%) at the time of diagnosis. Of the 88 patients, only 70 had evaluable CT scans for bronchus signs, with 59% of them having a bronchial sign image on the CT scan. There are 18 patients whose bronchus sign image could not be analyzed because there were no CT results in the electronic medical record, so they were removed from the analysis.

Ermayanti et al reported that men have a higher likelihood of developing lung cancer than women, with an incidence rate of 77.8% in men. The trend of lung cancer incidence in both sexes has fluctuated over the years. Additionally, multiple studies indicate that the 5-year survival rate is higher in women than in men.[26] Smoking, second-hand smoke, radon gas, asbestos, carcinogens, air pollution, and aging are risk factors for lung cancer. The higher incidence in men is mainly linked to smoking history.[27,28]

The incidence of lung cancer is highly age-related, with the highest rate among older people.[29] The age-based incidence increased sharply in the 45-49 years age group and decreased in the older age group. The highest incidence was in the 75-79 year age group for women and the 85-89 year old group for men. This aligns with our study, which also showed a significantly higher number of cases in individuals over 40 years old.[30]

In this study, we compared positive external histological results between groups of lesions measuring ≥3 cm and <3 cm based on CT scans performed by TBB bronchoscopy. There was no statistically significant difference in positive TBB results between the two groups, although the group of lesions with size ≥3 cm had a tendency to have a higher level of positivity when compared to the size lesions<3cm (OR=1.39; 95% CI=0.5364-3.779). However, this result is also not statistically significant (P>0.05) due to the small sample size and incomplete CT scan data in medical records.

Labbé et al, in their study, performed bronchoscopy with bronchial aspiration, brushing, and bronchoalveolar lavage (BAL) and found that the overall diagnostic yield increased with lesion size, reaching its peak at a diameter of 3 cm. Beyond this threshold, further increases in lesion size did not significantly enhance diagnostic performance.[31] Several recent technologies for guiding TBB, such as CT navigation, radial EBUS, electromagnetic navigation, robotic-assisted bronchoscopy, augmented fluoroscopy, and cone beam CT, have improved the positivity rates in sampling peripheral lung lesions.[22]

To assess the role of the bronchus sign regarding the positivity rate of TBB results, we divided the analysis into two separate groups: lesions ≥3 cm and lesions <3 cm. In the group of lesions ≥3 cm, the presence or absence of a bronchus

sign did not affect the positivity rate (OR=1.083; 95% CI=0.32–3.77; P=0.99). On the other hand, although not statistically significant (P=0.55), the presence of a bronchus sign in the group of lesions <3 cm showed a tendency to increase the positivity of TBB results (OR=4.5; 95% CI=0.45–66.62).

The size of the lesion influences the diagnostic yield, as does its visibility on fluoroscopy and the combination of diagnostic tools used. However, the criteria for classifying a lesion as small or large can vary between studies, which may affect the results. For example, Tateishi et al used 30 mm as the cutoff for tumor size, with a median size of 38 mm. Similarly, Sanchez-Font et al also applied a <30 mm threshold, whereas Boonsarngsuk et al and Ishid et al classified tumors as small when they were <20 mm.[25,32] Fluoroscopy in TBB can enhance diagnostic results by helping to more accurately determine the target area.[25]

The CT-BS has been shown to improve the diagnostic yield of peripheral lung lesions.[15] However, the clinical significance of the CT-BS remains controversial. Multiple studies suggest that the outcomes are affected by target lesion characteristics, including size, proximity to the hilum, and the presence of the CT-BS.[11] Ng et al reported that fluoroscopy-guided TBB achieved a diagnostic yield of approximately 83.4%, with a low overall complication rate, including pneumothorax. They emphasized the importance of adequate planning and preparation to minimize the risk of pneumothorax.[33]

Ost et al reported that TBB of peripheral lesions was diagnostic in 43.2% of cases. They also found that the overall diagnostic yield of bronchoscopy was 53.7%, with a sensitivity for lung cancer ranging from 60% to 74%. Additionally, they noted that the specimens obtained were usually adequate for diagnosing adenocarcinoma in 38.5% of patients.[34] The target location is not always visible on fluoroscopy and cannot always be precisely identified using fluoroscopy-guided bronchoscopy techniques, which can affect the diagnostic results.[35,36]

## CONCLUSION

The bronchus sign may increase TBB positivity, especially in peripheral lesions <3 cm. The size of the lesion also tends to influence the positivity rate of TBB. Larger lesions are generally associated with higher diagnostic yields. However, small sample size and missing CT data limited statistical significance.

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Original Article

# Severity of Obstruction Associated with Pulmonary Hypertension in COPD Patients at Arifin Achmad General Hospital: What Factors Influence?

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## Abstract

**Background:** Pulmonary hypertension can occur in stable chronic obstructive pulmonary disease (COPD) patients despite its unknown etiology or as a complication associated with other processes. Pulmonary hypertension was divided into five broad categories, including processes with common pathogenic mechanisms. The true incidence of pulmonary hypertension in COPD is unknown, as no systematically performed screening method can be widely used in COPD patients, while the mortality rate or complications from COPD are still very high.

**Method:** This study method was a cross-sectional study. This study was conducted on stable COPD patients who came to the pulmonary department at Arifin Achmad General Hospital to assess its association with the risk of pulmonary hypertension.

**Results:** This study involved 77 research subjects with the highest age <65 years (64.9%) with male gender (84.4%), airflow limitation degree GOLD II (moderate) (50.6%), severe Brinkman Index (76.6%), comorbid hypertension (7.8%), Asymmetric Dimethylarginine (ADMA)0 inflammatory marker including low-risk category (77.9%) and mild echocardiographic interpretation (75.3%). The Association of COPD severity was significant to the risk of pulmonary hypertension, the degree of airflow limitation (P=0.0001) and echocardiography interpretation (P=0.0001). At the same time, there was no significant association with ADMA levels (P=0.239). The Brinkman Index of smokers (P=0.006) was an important risk factor for pulmonary hypertension.

**Conclusion:** There was an association between COPD severity, echocardiographic interpretation and smoking status based on the Brinkman Index and the risk of pulmonary hypertension.

**Keywords:** COPD, ejection fraction, pulmonary hypertension, tricuspid regurgitation

## INTRODUCTION

Pulmonary hypertension (PH) is a functional disorder that occurs clinically. It is caused by pulmonary artery vascular disorders of unknown etiology. Pulmonary hypertension may also occur as a complication associated with other

processes.[1]

The classification of PH consists of five broad categories that include processes with common pathogenic mechanisms. Pulmonary hypertension due to pulmonary disease or hypoxia is group 3 of the PH classification. This third classification is the most common PH, with chronic obstructive pulmonary disease (COPD) being the most common cause.[1]

The prevalence of pulmonary hypertension in COPD patients varies depending on the diagnostic criteria used and the severity of COPD. According to a study by Thabut et al, pulmonary hypertension is found in approximately 30-50% of patients with advanced COPD.[1]

Another study by Chaouat et al reported that about 90% of COPD patients with chronic respiratory failure showed signs of mild to moderate pulmonary hypertension. In addition, a meta-analysis by Oswald-Mammosser et al. showed that mean pulmonary artery pressure (mean PAP) in COPD patients was in the range of 20-35 mmHg, with a significant proportion having mild pulmonary hypertension.[2]

Several factors have been identified as major contributors to the occurrence of pulmonary hypertension in COPD patients. The most dominant factor is chronic hypoxia, leading to pulmonary artery vasoconstriction and vascular remodeling.[3]

In addition, capillary loss due to alveolar destruction (as in emphysema), pulmonary hyperinflation and increased intrathoracic pressure also contribute to increased pressure in the pulmonary artery. Additional factors such as systemic inflammation, imbalance of vasodilators and vasoconstrictors (e.g., decreased nitric oxide (NO) and increased endothelin-1), and comorbidities such as sleep apnea or chronic pulmonary thromboembolism also aggravate the condition.[3]

Research on Asymmetric Dimethylarginine (ADMA) as a biomarker of pulmonary hypertension in patients with COPD is limited, especially in the context of the Indonesian population. However, several international studies have shown that elevated ADMA levels are associated with endothelial dysfunction and may contribute to the development of pulmonary hypertension.[4]

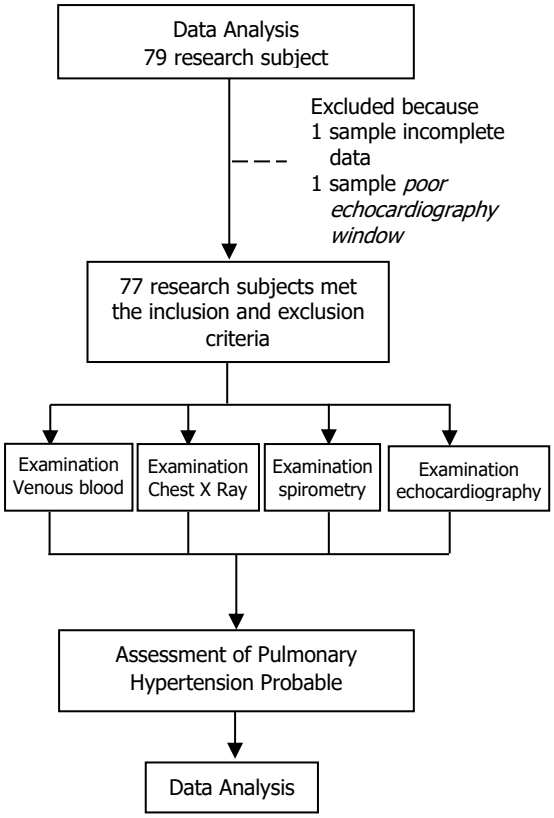
Asymmetric Dimethylarginine is an endogenous inhibitor of NO synthesis, which plays an important role in pulmonary vascular vasodilation. Increased levels of ADMA may lead to decreased NO production, which in turn causes vasoconstriction and vascular remodeling, two key mechanisms in the pathogenesis of pulmonary hypertension.[4]

In the context of COPD, frequent chronic hypoxia may increase ADMA production, thereby exacerbating endothelial dysfunction and accelerating the development of pulmonary hypertension. Nonetheless, more studies are needed to confirm the role of ADMA as a diagnostic or prognostic biomarker in COPD-related pulmonary hypertension.[5]

The aim research was to analyze the severity of COPD with probable pulmonary hypertension and its influencing factors at Arifin Achmad General Hospital.

## METHOD

This study was a descriptive-analytic study using a cross-sectional research design. The study was conducted at Arifin Achmad Regional General Hospital from January 2023 to March 2023. The population of this study was stable COPD patients (mild to severe according to GOLD) who came to Arifin Achmad General Hospital and met the inclusion and exclusion criteria.




Inclusion criteria consisted of patients with mild to severe stable COPD, both male and female, who came to the pulmonary clinic or who were admitted to Arifin Achmad General Hospital, aged 18 to 85 years, and willing to voluntarily participate in all stages of the study by giving written consent and signing an informed consent form. Exclusion criteria consisted of patients with poor echocardiography windows on examination, patients with acute coronary syndrome, patients diagnosed with moderate to severe mitral stenosis, and patients with lung parenchyma and pleura abnormalities from the results of thoracic photographs.

Data were collected after screening the subjects according to the inclusion and exclusion criteria. In this study, a total sample size of 79 subjects was obtained. A total of 2 subjects were excluded because one sample had incomplete patient data, and another had a poor echocardiography window. The total sample was 77 people. Statistical analysis application used SPSS version 25.

The analysis of this study was divided into univariate and bivariate. The univariate analysis consisted of the characteristics of the study subjects and the Tricuspid Regurgitation description of the study subjects. In contrast, the bivariate analysis consisted of the association between COPD severity (airflow limitation, ADMA inflammatory marker, and Tricuspid Regurgitation degree) to probable pulmonary hypertension and the association between risk factors to probable pulmonary hypertension. The value of $P<0.05$ indicates a statistically significant.

Spirometry using the CHEST$^{R}$ brand and echocardiography using the Hilips Healthcare brand EPIQ$^{R}$ 7. The measurement of ADMA levels in this study was performed using venous blood samples. Asymmetric Dimethylarginine is

often categorized into three concentration levels—low, moderate, and high—based on plasma concentration values. These categories are typically used in the context of clinical research or diagnosis to assess cardiovascular risk or endothelial dysfunction.

A volume of 5 ml of peripheral venous blood was drawn from each subject, collected in a plain vacutainer tube, and allowed to clot at room temperature. The samples were then centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum was stored at -20°C until analysis.

The quantification of serum ADMA levels was carried out using the enzyme-linked immunosorbent assay (ELISA) method, following the manufacturer's instructions, CUSABIO®. The ELISA kit used was specific for human ADMA and had a detection range of approximately 0.05–10 µmol/L. This study is approved by the ethical committee of Arifin Achmad General Hospital, with research ethics code number B/005/UN19.5.1.1.8/UEPKK/2023.

## RESULT

The characteristics of COPD patients in this study are shown in Table 1. This study found that most age of COPD patients was <65 years old, as many as 50 people (64.9%), the severity of COPD was predominantly GOLD II (moderate) 39 people (50.6%), the degree of smoking (index Brinkman (IB)) was heavy 59 people (76.6%), the most comorbid hypertension 7 people (9.1%), the most ADMA levels included low risk 60 people (77.9%).

In this study, the frequency of interpretation of tricuspid regurgitation (TR) in COPD was mostly mild 58 subjects (75.3%), followed by moderate 14 subjects (18.2%) and severe 5 subjects (6.5%). Echocardiographic interpretation consists of the appearance of the right ventricle, right atrium, pulmonary artery, and superior vena cava.

Table 1. Characteristics of research subjects

| Variable | n (%) |
|---|---|
| Age | |
| <65 years | 50 (64.9%) |
| ≥65 years old | 27 (35.1%) |
| Gender | |
| Male | 65 (84.4%) |
| Female | 12 (15.6%) |
| Severity of COPD | |
| GOLD I (mild) | 2 (2.6%) |
| GOLD II (moderate) | 39 (50.6%) |
| GOLD III (severe) | 32 (41.6%) |
| GOLD IV (very severe) | 4 (5.2%) |
| Smoker's Brinkman Index | |
| Mild BI | 2 (2.6%) |
| Moderate BI | 16 (20.8%) |
| Severe BI | 59 (76.6%) |
| Comorbidities | |
| Diabetes Mellitus | 3 (3.9%) |
| Hypertension | 7 (9.1%) |
| No comorbidities | 67 (87.0%) |
| Inflammation marker (ADMA) | |
| Low risk | 60 (77.9%) |
| Moderate risk | 11 (14.3%) |
| High risk | 6 (7.8%) |
| Normal | 0 (0.0%) |

The association between the severity of COPD based on airflow limitation (GOLD criteria) with probable pulmonary hypertension seen from the results of echocardiography was shown in Table 2. In GOLD I (mild), all had mild risk, as many as 2 people (100.0%). GOLD II (moderate)

most had a mild risk of 25 people (64.1%). In contrast to GOLD I and GOLD II, the most moderate risk in GOLD III (severe) was 23 people (71.9%).

Global Initiative for Chronic Obstructive Lung Disease IV (very severe) had a severe risk for probable pulmonary hypertension in as many as 4 people (100.0%). There is a significant Association between the severity of COPD based on GOLD with probable pulmonary hypertension, with P<0.05.

Asymmetric Dimethylarginine levels from the low-risk category to the highest probable pulmonary hypertension moderate risk were found in 30 people (50.0%). Asymmetric Dimethylarginine levels were found in 60 people at low risk, 11 at moderate risk, and 6 at high risk. There was no significant Association between ADMA levels and probable pulmonary hypertension, where the P>0.05 could be seen in Table 2.

The association between COPD risk factors to probable pulmonary hypertension was shown in Table 2. For patients below 65 years old, there was no difference between the mild and moderate risk of probable pulmonary hypertension, namely 20 people (40.0%), with P=0.267.

Table 2. Association between the severity of COPD based on airflow limitation (GOLD criteria), Inflammatory Marker ADMA and Inflammatory Marker ADMA with probable pulmonary hypertension seen from the results of echocardiography

| Variable | Probable Pulmonary Hypertension | | | P |
|---|---|---|---|---|
| | Mild Risk | Moderate Risk | Severe Risk | |
| Severity of COPD based on spirometry | | | | |
| GOLD I (mild) | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0.0001[b] |
| GOLD II (moderate) | 25 (64.1%) | 14 (35.9%) | 0 (0.0%) | |
| GOLD III (severe) | 0 (0.0%) | 23 (71.9%) | 9 (28.1%) | |
| GOLD IV (very severe) | 0 (0.0%) | 0 (0.0%) | 4 (100.0%) | |
| ADMA Inflammatory Markers | | | | |
| Low risk | 22 (36.7%) | 30 (50.0%) | 8 (13.3%) | 0.239[b] |
| Moderate Risk | 4 (36.4%) | 3 (27.3%) | 4 (36.4%) | |
| High Risk | 1 (16.7%) | 3 (50.0%) | 2 (33.3%) | |
| Age | | | | |
| <65 years | 20 (40.0%) | 20 (40.0%) | 10 (20.0%) | 0.267[a] |
| ≥65 years old | 7 (25.9%) | 16 (59.3%) | 4 (14.8%) | |
| Gender | | | | |
| Male | 23 (35.4%) | 33 (50.8%) | 9 (13.8%) | 0.240[b] |
| Female | 4 (33.3%) | 3 (25.0%) | 5 (41.7%) | |
| Brinkman index (BI) Smokers | | | | |
| Mild BI | 2 (100.0%) | 0 (0.0%) | 0 (0.0%) | 0.006[a] |
| Moderate BI | 10 (62.5%) | 4 (25.0%) | 2 (12.5%) | |
| Severe BI | 15 (25.4%) | 32 (54.2%) | 12 (20.3%) | |
| Comorbidities | | | | |
| Diabetes Mellitus | 1 (33.3%) | 2 (66.7%) | 0 (0.0%) | 0.126[b] |
| Hypertension | 0 (0.0%) | 4 (57.1%) | 3 (42.9%) | |
| No comorbidities | 26 (38.8%) | 30 (44.8%) | 11 (16.4%) | |

Note: [a]Chi-square test; [b]Uji Fisher Test

Table 3. Association of Inflammatory Marker ADMA with COPD Severity

| Degree of ADMA | COPD Severity | | | | P |
|---|---|---|---|---|---|
| | GOLD I (Mild) | GOLD II (Moderate) | GOLD III (Severe) | GOLD IV (Very severe) | |
| Low risk | 2 (3.3%) | 32 (53.3%) | 24 (40.0%) | 2 (3.3%) | |
| Moderate risk | 0 (0.0%) | 5 (45.5%) | 5 (45.5%) | 1 (9.1%) | 0.373* |
| High risk | 0 (0.0%) | 2 (33.3%) | 3 (50.0%) | 1 (16.7%) | |

Note: *Uji Fisher Test

At the age of ≥65, the highest probable pulmonary hypertension at moderate risk was 16 people (59.3%). Male have the highest risk for pulmonary hypertension, namely moderate risk, 33 people (50.8%), and female, the severe risk, is the highest risk for probable pulmonary hypertension, 5 people (41.7%).

Based on smoking status, Brinkman index (BI), mild BI and moderate BI had the highest risk of probable pulmonary hypertension (100.0% and 62.5%). The most severe BI had a moderate risk of 32 people (54.2%). The most common comorbidities in this study were hypertension, with 4 participants having moderate risk for PH (57.1%), followed by type II DM, with 2 participants in moderate risk for PH (66.7%). There was a significant Association between BI smokers and the incidence of probable pulmonary hypertension in COPD patients, with P<0.05.

The association between ADMA and the severity of COPD is presented in Table 3. In the low-risk ADMA category, there were 32 people (53.3%) in GOLD II. Moderate risk ADMA was found in GOLD II and GOLD III (5 people; each 45.5%). The high-risk ADMA category was found in GOLD III in as many as 3 people (50.0%). There was no significant association between the degree of ADMA and the severity of COPD, with P=0.373.

## DISCUSSION

Chronic obstructive pulmonary disease is a preventable and treatable lung disease characterized by persistent and generally progressive airflow limitation, airway and/or alveoli abnormalities due to harmful gases or particles, influenced by host factors and abnormal lung development, exacerbations and comorbidities contribute to the severity of the disease. Chronic obstructive pulmonary disease patients with age <65 years old in this study had a greater proportion than ≥65 years old. This result aligns with Muzlifa et al's and Nugraha's research, where most were <65 years old.[6,7]

Different results were found in The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO), which estimated that the prevalence of COPD increased gradually with age, with the highest being >60 years old. The prevalence of COPD is two to three times higher in people over 60 years old compared to younger age groups. COPD has been considered a condition of accelerated lung aging.[3,8]

The most common gender in this study was male. These results align with

Hariyanti's research, where the highest proportion of COPD sufferers was male.[9] Tabar's research also obtained the same results, mostly in males.[10] The prevalence of males suffering from COPD is three times higher than females in Indonesia.[8]

This is due to the habit of smoking more among males. The prevalence of COPD increases with smoking status, and only 4% showed the presence of other risk factors, such as passive smoking or occupational exposure factors.[3] Riskesdas data in 2018 showed that the prevalence of smokers in Indonesia was 16 times higher in males (65.8%).[2]

Chronic obstructive pulmonary disease patients, based on GOLD criteria in this study, were mostly in the GOLD II group. These results align with Marco's research in Spain, where most COPD patients were in the GOLD II population.[3] In contrast to Salawati's research, the classification of COPD patients was mostly in the GOLD III group.[11] The severity of COPD is associated with increased mortality and hospitalization.[12] However, the development of the severity of COPD disease in the early stages has no significant difference in health status.[4]

Husnah's research found an association between the severity of COPD and malnutrition in COPD patients and was associated with an increased risk and frequency of acute exacerbations.[13] The higher the severity of COPD, the higher the metabolism. The type of metabolism referred to is increased energy metabolism (hypermetabolism), specifically due to the increased work of breathing in patients with COPD, particularly in moderate to severe stages (GOLD II and above).[10]

Due to the increased energy expenditure associated with labored breathing, individuals with COPD often experience insufficient caloric and protein intake, leading to compromised nutritional status. The increase in energy needs due to increased work of the respiratory musculature, due to chronic hypoxemia causes hypermetabolism.[14] This study was mostly GOLD II because stable COPD dominated the study sample.

Smoking status in this study was mostly in the heavy BI group. These results align with Nugraha's and Salawati's research, where most were heavy BI.[7,11] In contrast to the study by Muzlifa et al, most COPD with moderate BI (46.7%).[6] The moderate and heavy smokers group had 8 times higher risk of experiencing COPD compared to the light smokers group.[7]

The association between smoking and COPD depends on the dose/number of cigarettes and the airway response, where the risk of COPD increases with the number of cigarettes smoked daily and the longer the smoking habit.[15] Bronchoalveolar fluid samples from COPD smokers show that smoking contributes significantly to morbidity and mortality, with an increase in the number of macrophages and neutrophils in smokers compared to non-smokers.[8]

The most common comorbidity in this study was hypertension. This is similar to the study by Imaizumi et al shows that hypertension is the most prevalent comorbid in COPD patients.[8] COPD causes

the thickening of the airways and stiffness of blood vessels, thus reducing the amount of oxygen entering the lungs. This can cause the arteries around the lungs to narrow and risk of hypertension. Vascular stiffness may also result in increased sympathetic nerve activity. Air pollution can also be a risk for decreased arterial blood vessel development and morning hypertension, both of which can worsen atherosclerosis.[3]

The most common ADMA inflammatory markers in this study were in the low-risk group. ADMA levels will increase along with the severity of COPD. The study by Parmaksiz et al found that the average ADMA level was 0.11 µmol/L in GOLD I, 0.18 µmol/L in GOLD II, 0.19 µmol/L in GOLD III, and 0.23 µmol/L in GOLD IV.[4] Oxidative stress in COPD can increase the activity of arginine methylation enzymes that produce inhibitors of ADMA.[3]

Increased ADMA concentrations are associated with increased pulmonary artery pressure (PAP) measurements in COPD patients.[3] The low-risk group was the most common because the study sample was also predominantly in the GOLD II (moderate) population, so the risk for endothelial dysfunction was also not too high.

There is no data on the distribution of tricuspid regurgitation in COPD patients. These results align with found that almost 50% of COPD patients had varying degrees of tricuspid valve disorders.[6] Increasing degrees of COPD and lung hyperinflation have also been associated with worsening tricuspid regurgitation (TR) severity.[16] Severe and very severe COPD patients have been shown to have structural changes in the right heart, which can ultimately lead to the development of pulmonary hypertension.[17]

This study population consisted mostly of mild TR because stable COPD dominated the COPD sample with GOLD II (moderate), so the picture of tricuspid regurgitation was mostly in the mid-TR condition. Tricuspid regurgitation is associated with lower survival, regardless of left ventricular ejection fraction (LVEF) or pulmonary hypertension. Several studies have confirmed a close association between pulmonary artery pressure estimated by tricuspid regurgitation in COPD patients.[17]

This study found that the most common severity of COPD (GOLD criteria) was in GOLD II, and the higher the severity of COPD, the greater the risk of pulmonary hypertension. Moderate risk of pulmonary hypertension is the most apparent in GOLD III and IV. All patients in these groups have a high risk for the incidence of pulmonary hypertension. The severity of COPD is directly proportional to the incidence of pulmonary hypertension; the largest percentage of patients with pulmonary hypertension was in GOLD IV, followed by GOLD III. Severe pulmonary hypertension only occurs in severe or very severe COPD.[17]

The overall incidence of pulmonary hypertension in COPD, and this rate was directly proportional to the severity of COPD. In contrast to this study, although

Aguirre-Franco's study found the highest frequency of COPD degree was the very severe category, both found a significant Association between the severity of COPD and the incidence of pulmonary hypertension.[17] These results align with the theory that pulmonary hypertension occurs along with the severity of COPD. The higher the severity of COPD, the higher the probable pulmonary hypertension caused by chronic hypoxemia.

The main pathophysiological cause of pulmonary hypertension is chronic alveolar hypoxia. Chronic hypoxia and hypoxemia, systemic inflammation, atherosclerosis, and pulmonary artery endothelial dysfunction lead to increased pressure in the pulmonary artery, therefore triggering pulmonary hypertension.[17]

Pulmonary hypertension is a significant risk factor for hospitalization and is associated with shorter life expectancy. Residential location also affects the incidence of pulmonary hypertension. There is a higher risk of developing pulmonary hypertension in COPD patients who live in the highlands compared to the lowlands, despite having the same severity of COPD based on the same GOLD criteria.[17]

This study identified three categories of risk based on Asymmetric Dimethylarginine (ADMA) levels: low, moderate, and high risk. Both the low-risk and high-risk ADMA groups were most commonly associated with a moderate risk of developing pulmonary hypertension. Interestingly, the moderate-risk ADMA group showed a more variable distribution, with equal proportions (36.4%) experiencing either mild or severe risk of probable pulmonary hypertension.

These results align with Aguirre-Franco's research, where higher ADMA levels (high risk) in COPD patients are significantly associated with the incidence of pulmonary hypertension.[17] There is not much research data regarding the Association between ADMA levels and the incidence of pulmonary hypertension. However, ADMA has emerged as a risk marker for many conditions related to pulmonary hypertension.[4]

Asymmetric dimethylarginine is an endogenous competitive inhibitor of nitric oxide (NO) synthase. L-Arginine metabolism, including NO synthesis pathways and arginase, is important in maintaining airway function.s[18] The lungs produce significant amounts of ADMA. ADMA levels are associated with the severity of vascular endothelial damage. A study shows that AMDA levels are associated with the incidence and severity of asthma and cystic fibrosis. Parmaksız's study found that ADMA levels were proportional to the severity of COPD based on GOLD criteria. The higher the severity of COPD, the higher the ADMA levels. FEV1 tends to decrease as ADMA concentration increases.[4]

The degree of ADMA levels of this study was mainly dominated by GOLD II in the low-risk group, GOLD II and GOLD III in the moderate-risk group, and GOLD III in the high-risk group. There was no significant association between the degree

of ADMA and the severity of COPD. These results align with a study by Ozkarafakili, where the degree of ADMA is proportional to the severity of COPD; the higher the ADMA levels, the higher the severity of COPD.[19]

The same thing is also found in a study by Zinellu, where increasing ADMA levels and the ADMA/arginine ratio (mainly due to reduced arginine concentration) are directly proportional to the severity of COPD.[20] In theory, ADMA in the COPD airway causes a functionally relevant shift of l-Arginine breakdown by NO synthase.[18] This study was mostly at low risk because the study sample was dominated by GOLD II COPD (moderate degree).

This study found that age <65 years had the highest risk of pulmonary hypertension, namely mild and moderate risk, while at age ≥65 years, the most prevalent for pulmonary hypertension was the moderate risk group. There is no significant association between age and the risk of pulmonary hypertension. This result is different from the study that found an increase in the prevalence of up to 10 times at the age of ≥65 years. The prevalence of pulmonary hypertension increases with age. Other studies also found the prevalence of pulmonary hypertension in COPD at a median age of 68.1 years.[21]

Even higher mean age in stable COPD subjects with pulmonary hypertension of 71.1±11.8 years compared to COPD without pulmonary hypertension of 63.7±10.2 years.[22] The different results in this study were because the sample was dominated by age <65 years.

In this study, males were most commonly associated with a moderate risk of developing pulmonary hypertension, whereas females had the highest risk in the severe category. There is no significant association between gender and the risk of pulmonary hypertension. This result aligns with a study by Mohammed that the incidence of pulmonary hypertension is unrelated to gender.[22]

Basak et al found that 95% of male subjects had stable COPD and impaired cardiac function.[23] This result also aligns where female gender is a probable pulmonary hypertension factor, even though females with this condition can survive better than males.[20] This is because females with pulmonary hypertension or those associated with connective tissue have higher cardiac output and lower pulmonary vascular resistance.[24]

The Brinkman index of COPD in this study was statistically associated with probable pulmonary hypertension, where mild BI and moderate BI had a low risk for pulmonary hypertension, while severe BI had the highest at moderate risk. There is no research data regarding the Brinkman index on probable pulmonary hypertension.

The study by Mohammed found that 30.8% of smokers had pulmonary hypertension, but not statistically significant.[22] Smoking causes an acute increase in blood pressure and heart rate. Smoking is also a major contributor to the

development of COPD, chronic bronchitis, and emphysema, which are diseases correlated with secondary pulmonary hypertension.[8]

Chronic obstructive pulmonary disease and cardiovascular disorders have been recognized as shared risk factors for smoking. Cigarette smoke has increased the risk of atherosclerosis and the systemic inflammatory response. The inflammatory state in COPD occurs due to the adhesion of leukocytes and other molecules to the endothelium, damaging the endothelial wall and forming atherosclerotic plaques.[8]

Cigarette smoke is associated with pulmonary hypertension in humans and animal models. Although the etiology of pulmonary hypertension in smokers is not understood, some studies suspect a role in inducible nitric oxide synthesis (iNOS) and oxidative vascular damage in inducing oxidative stress.[8]

Among the comorbidities identified in COPD patients—namely diabetes mellitus, hypertension, and hypertensive heart disease—hypertension was the most common. It was also the only comorbidity significantly associated with a high risk of developing pulmonary hypertension. In contrast, diabetes mellitus and hypertensive heart disease were not associated with an increased risk.[8]

Cardiovascular disease, hypertension and COPD are correlated with each other, and it is difficult to adjust the risk factor of smoking as the cause of one of the above conditions.[8] Hypertension, as a risk factor for cardiovascular disorders, will also adversely affect the prognosis and mortality in COPD. Possible Association mechanisms between COPD and hypertension are systemic inflammatory conditions, chronic hypoxia, and hypercapnia due to airway obstruction, causing increased intrathoracic pressure.[25]

The limitation of this study was that the sample was dominated by moderate severity of COPD, so a larger and heterogeneous sample was needed to assess the degree of risk of pulmonary hypertension. Additionally, this study design is cross-sectional and the data of this study were retrieved from medical records. It is suggested to conduct a cohort study design to establish the association between COPD and pulmonary hypertension.

## CONCLUSION

These findings indicate that pulmonary hypertension in COPD is strongly correlated with the degree of airflow obstruction, which is likely mediated by chronic hypoxia, pulmonary vascular remodeling, and systemic inflammatory response.

Although ADMA is known to be an endogenous inhibitor of nitric oxide synthase that may affect endothelial function, the results of this study suggest that the role of ADMA as a biomarker of pulmonary hypertension in COPD has not been significantly proven, so further studies with more heterogeneous samples and longitudinal designs are needed for evaluation of causal relationships.

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Original Article

# Mortality Audit In COVID-19 Cases of the Omicron Variant in Persahabatan Hospital

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## Abstract

**Background:** SARS-CoV-2, the virus that causes COVID-19, has mutated into various variants. Deaths in COVID-19 cases caused by the Omicron variant had the highest rate compared to other variants. This research aims to mortality audit of the Omicron variant of COVID-19 in 2022 at Persahabatan Hospital.

**Method:** This is a cross-sectional observational study focusing on the death audit form recommended by the official Indonesian Hospital Association. Used data from Medical Cause of Death Certificate (SMPK) and medical records of patients treated and died at Persahabatan Hospital in January-December 2022. The causes of death (COD) from the audit results were compared with SMPK. Conducted interviews with the doctor who takes care of patients to explore the root of the problem and improvement efforts.

**Results:** Of the 568 COVID-19 patients with the Omicron variant hospitalized, 130/568 died. As many as 42.52% of the COVID-19 variant Omicron patients died from COVID-19 and 57.48% had COVID-19. The three most COD were respiratory failure, MOF and septic shock. The three underlying COD were COVID-19, bacterial pneumonia and lung cancer. The COD in SMPK and the results of the mortality audit are only appropriate for 23.62%. The best three suggestions for improving clinical management are evaluating the patient supervision/monitoring system, testing for COVID-19 antigens carried out earlier before PCR, and providing special services for COVID-19 patients with comorbid. The top three suggestions for improving hospital managerial aspects are to create and evaluate a special SOP for COVID-19 patients with comorbid, add special service facilities for COVID-19 patients with comorbid and increase ICU bed capacity and human resources.

**Conclusion:** The COVID-19 variant Omicron patients died due to COVID-19 and had COVID-19. The three most COD were respiratory failure, MOF and septic shock. Only 23.62% of COD from SMPK were consistent with the results of the mortality audit.

**Keywords:** COVID-19, immediate cause, mortality audit, Omicron, underlying cause

## INTRODUCTION

Coronavirus Disease 2019(COVID-19) is a disease caused by infection with the SARS-CoV-2 virus. The virus was first identified in Wuhan, China, in December 2019 and then spread throughout the world. In March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic.[1]

During this pandemic period, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has experienced mutations and produces various variants. One of the SARS-CoV-2 variants is the Omicron variant (B.1.1.529), which was first reported in South Africa on November 24, 2021. The death rate for the Omicron variant is also lower than the Delta variant. Data from the United States and South Africa shows that the case fatality ratio for the Omicron variant is two times lower than for the Delta variant.[1]

Hospitals, as one of the providers of health services, need to make efforts to maintain service quality. In an effort to maintain the quality of service in health facilities, the concept of clinical governance, which can be defined as a framework in which health service organizations are responsible for continuously improving the quality of their services and maintaining high service quality, can be applied.[2]

Efforts to prevent morbidity and mortality in hospitals are one of the main components in providing safe services in health facilities. This can be achieved through meetings and discussions related to morbidity and mortality, which are carried out routinely in hospitals to identify unwanted events and deaths. Death audits of death cases that occur in hospitals can also be a method for identifying various causes of death and efforts to prevent them in the future.[2]

Death audits are useful in preventing and reducing death rates in hospitals, but their implementation still faces various obstacles.[3] Another challenge in death audits that is often faced is the incompleteness or mismatch of the cause of death written on the Medical Cause of Death Certificate (*Sertifikat Medis Penyebab Kematian*/SMPK) with the cause of death obtained in the death audit. A study at Persahabatan Hospital of lung cancer patients found that more than half (55.2%) of the death sheets did not match the medical record and 61.5% of the death sheet writing did not comply with the SOP.[4]

Persahabatan Hospital, as the National Respiratory Center, has become a national referral hospital for COVID-19 cases. During the emergency response period, the spike in COVID-19 cases in early 2022 was dominated by the Omicron variant. The COVID-19 death rate that occurred at Persahabatan Hospital was quite high during the emergency response period for the spike in COVID-19 cases in early 2022 (18.54%). However, whether deaths that occur in patients treated with or because of COVID-19 are caused by COVID-19 as the underlying cause or due to other causes still needs to be further evaluated through death audit activities.

This research aims to conduct an audit of death cases related to the COVID-19 variant Omicron during 2022. It is hoped that with the death audit, the basic cause and direct cause of death in cases of COVID-19 variant Omicron who died at Persahabatan Hospital will be known, and it will be known whether the death was avoidable or not avoidable, what is the level of conformity between the causes of death listed in the Medical Cause of Death Certificate (SMPK) and those determined through the death audit as well as suggestions for improvement efforts that can be made in the future from the results of the death audit carried out.

## METHOD

This is an observational study with a cross-sectional research design. Secondary data from SMPK and medical records of patients who died while being treated at National Respiratory Center Persahabatan Hospital from January 2022 to December 2022 were extracted. Death audits were done using the form recommended by the official Indonesian Hospital Association.[5] The causes of death from the audit results were compared with SMPK.

The research also took qualitative data by interviewing the doctor who takes care of the patient/*dokter penanggung jawab pasien* (DPJP), to explore the root of the problem and improvement efforts that could be made. Inclusion criteria are confirmed COVID-19 patients, age greater than or equal to 15 years, Whole Genome Sequence (WGS) results in variant Omicron or if there are no WGS results, positive Spike Gene Target Failure (SGTF) results.

The sampling method is the total sampling method. The research instruments were the COVID-19 death audit form recommended by the official Indonesian Hospital Association,[5] an interview form and the Medical Cause of Death Certificate (SMPK) form. The research has received ethical approval from the Health Research Ethics Committee of Persahabatan Hospital with number 0039/KEPK-RSUPP/02/2024.

## RESULT

A total of 1580 COVID-19 patients were hospitalized between January to December 2022 at Persahabatan Hospital. Of the 1580, there were 568 patients with COVID-19 variant Omicron or probable Omicron, 298 patients were non-Omicron, 676 had no data on SGTF and/or WGS results and 38 patients were not tested for SGTF.

Of the 568 COVID-19 variant Omicron or probable Omicron patients who were treated, 130 patients died and 438 patients recovered and went home after being treated. From the data above, the proportion of COVID-19 variant Omicron patients who died while being treated at Persahabatan Hospital was 130/568 (22.89%).

Men (86 subjects, 67.7%) are the most common sex found compared to women subjects (41 subjects, 32.2%). From the age aspect, the majority were elderly (>60 years), namely 69 subjects

(54.3%), followed by adults (19-60 years) with 55 subjects (43.3%).

The most common occupations include private employees with 34 subjects (26.8%), housewives (IRT) with 28 subjects (22.0%) and entrepreneurs with 21 subjects (16.5%). For nutritional status determined by body mass index (BMI), the majority were above normal, as many as 58 subjects (45.7%), consisting of overweight as many as 18 subjects (14.2%) and obesity as many as 40 people (31.5%).

Based on clinical data, the majority of subjects in this study had never received a COVID-19 vaccination, namely 53 subjects (41.7%), followed by subjects who had received two vaccinations, 45 subjects (35.4%). There were 17 subjects (13.4%) who had received more than 2 vaccinations and 12 subjects (9.4%) who had only received the vaccine once.

Almost all subjects, namely 114 subjects (89.8%), underwent treatment for less than 14 days at Persahabatan Hospital until they died. Meanwhile, the most common comorbidities found were hypertension in 55 subjects (43.3%); diabetes mellitus as many as 47 subjects (37.0%); kidney disease in 41 subjects (32.3%); heart disease as many as 30 subjects (23.6%); and cancer as many as 24 subjects (18.9%).

The majority of research subjects who came/were referred to Persahabatan Hospital for treatment were already in a critical condition of COVID-19 (52 subjects, 40.9%), followed by a moderate degree of COVID-19 (37 subjects, 29.1%). Based on the type of ward, more subjects were treated in the ICU (65 subjects, 51.2%) while the remainder were treated in non-ICU COVID-19 isolation wards (62 subjects, 48.8%).

The death audit carried out finds the underlying cause of death, the immediate cause of death, and the indirect cause of death (COD). Analysis of the death audit conducted showed that the three most immediate causes of death were respiratory failure with 49 cases (38.58%), multiple organ failure (MOF) with 33 cases (25.98%) and septic shock with 21 cases. (16.54%). The complete direct causes of death according to the audit results can be seen in Table 1.

Table 1. Immediate causes of death according to audit results (n=127)

| List of immediate COD | n | % |
|---|---|---|
| Respiratory Failure | 49 | 38.58 |
| Multiple organ failure (MOF) | 33 | 25.98 |
| Septic shock | 21 | 16.54 |
| Acute heart failure (include cardiac arrest) | 10 | 7.87 |
| Cardiogenic shock | 5 | 3.94 |
| Acute respiratory distress syndrome (ARDS) | 3 | 2.36 |
| Circulatory failure (include shock) | 2 | 1.57 |
| Aspiration | 1 | 0.79 |
| Hepaticum coma | 1 | 0.79 |
| Non-ST-segment Elevation Myocardial Infarction (NSTEMI) | 1 | 0.79 |
| Hemorrhagic shock | 1 | 0.79 |

Meanwhile, the 3 (three) underlying causes of death were COVID-19 with 54 cases (42.52%), bacterial pneumonia with 24 cases (18.90%) and tumor/lung cancer with 16 cases (12.59%) (Table 2).

The results of further analysis from the death audit process found that there were 102 cases of COVID-19 variant Omicron deaths that were not avoidable

and 25 cases of deaths of COVID-19 variant Omicron that were avoidable. Of the 25 avoidable cases, 9 were avoidable cases related to late detection of the cause of death, while 25 cases were related to inadequate or suboptimal management.

Table 2. Underlying Causes of Death According to Audit Results (n=127)

| List of Underlying COD | n | % |
|---|---|---|
| COVID-19 | 54 | 42.52 |
| Bacterial Pneumoniae | 24 | 18.90 |
| Lung Tumor/Cancer | 16 | 12.59 |
| Coronary Heart Disease | 3 | 2.36 |
| Acute Lymphoid Leukemia (ALL) | 2 | 1.57 |
| Asphyxia | 2 | 1.57 |
| Bacterial Infection | 2 | 1.57 |
| Chronic Kidney Disease (CKD) | 2 | 1.57 |
| Chronic Hepatitis B | 2 | 1.57 |
| Cerebellar tumor/mass | 2 | 1.57 |
| Decubitus ulcus | 2 | 1.57 |
| Acute limb ischaemic | 1 | 0.79 |
| Infected Bronchiectasis | 1 | 0.79 |
| Carcinoma colon | 1 | 0.79 |
| Carcinoma mammae | 1 | 0.79 |
| Carcinoma tiroid | 1 | 0.79 |
| Catheter-related bloodstream infection (infected CDL) | 1 | 0.79 |
| Cerebrovascular disease (CVD) | 1 | 0.79 |
| Enterocutan fistulla | 1 | 0.79 |
| Gangrene | 1 | 0.79 |
| Neuroendocrine carcinoma, high grade | 1 | 0.79 |
| Meningoensefalitis bacterial | 1 | 0.79 |
| Trauma Multiple | 1 | 0.79 |
| Osteosarcoma st. IV | 1 | 0.79 |
| Peritonitis | 1 | 0.79 |
| Chronic Obstructive Pulmonary Disease | 1 | 0.79 |
| Atrioventricular (AV) Block | 1 | 0.79 |

The root of the problem with late detection of the cause of death was a lack of alertness, so that it did not predict worsening from the start, 4 (33.3%). Next, there were 2 patients (16.67%) who assessed the Early Warning System (EWS) which was not appropriate to the patient's clinical condition, 2 patients (16.67%) reported late detection of COVID infection due to decreased alertness and 2 patients (16.67%) reported that patient supervision was less than optimal (both in terms of monitoring aspects and whether monitoring devices were not installed) there were 2 patients (16.67%) (Table 3).

Meanwhile, the root of the problem of inadequate management is that the hospital ICU room is full as many as 6 (13.04%), patients in end-stage or DNR condition, so that the ICU is not a priority as many as 4 (8.69%), facilities for special management of COVID-19 are less than optimal as many as 3 (6.52%). There were 3 (6.52%) late for consult to the ICU or late ACC from the ICU, 3 (6.52%) were given late antivirals and 3 (6.52%) had poor general condition due to severe comorbidities (Table 4).

In assessing the suitability of the causes of death listed in the SMPK with the results of the death audit, it showed that only 30 patients (23.62%) were appropriate and the remaining 97 patients (76.38%) were not appropriate. The correspondence between SMPK and death audits is still quite low, namely only 23.62% for direct causes of death, 14.96% for indirect causes of death (intermediate causes of death) and 51.97% for the basic cause of death.

From interviews with DPJP, many suggestions were obtained for improving future services at Persahabatan Hospital. This improvement proposal is divided into clinical management aspects and

managerial aspects. The most frequent suggestion for improving patient clinical management was evaluation of the patient supervision/monitoring system (13 DPJP).

Then, the second most proposed improvement in clinical management is the COVID-19 antigen examination carried out as a first step before the COVID-19 PCR examination to detect COVID-19 infection more quickly. This suggestion was from 5 DPJP. The third most common suggestion for clinical improvement is the need to provide special services for patients with COVID-19 (bronchoscopy, PCI, HD).

Several DPJPs proposed increasing the number of High Flow Nasal Cannula (HFNC) in hospitals. One of the many suggestions is the need to periodically discuss serious/emergency cases with a multidisciplinary team (DPJP, PPRA and related parties) with 3 DPJPs each. Complete suggestions for improving clinical management are in Table 6.

Table 3. The root of the problem late detection of the causes of death

| The root of the problem late detection of the causes of death | n | % |
|---|---|---|
| Lack of alertness, not predicting earlier | 4 | 33.3 |
| Writing an EWS is not clinically appropriate | 2 | 16.67 |
| Late COVID screening/awareness of COVID infection falls | 2 | 16.67 |
| Patient supervision is less than optimal (both in terms of supervision aspects, and the monitoring equipment is not installed) | 2 | 16.67 |
| Difficulty monitoring patients (monitoring fluid balance in CKD patients on HD) | 1 | 8.3 |
| Patient management before referral is not optimal. | 1 | 8.3 |

Table 4. The root of the problem of inadequate management

| The root of the problem of inadequate management | n | % |
|---|---|---|
| The ICU room is full | 6 | 13.04 |
| End-stage disease or DNR patients are not ICU priority | 4 | 8.69 |
| Special treatment facilities for COVID are not available (PCI, radiotherapy) | 3 | 6.52 |
| Late/not consulted ICU/late approval from ICU | 3 | 6.52 |
| Antivirus has not been given because we are waiting for the PCR results | 3 | 6.52 |
| Poor general condition, severe comorbidities | 3 | 6.52 |
| Monitoring is less than optimal | 3 | 6.52 |
| COVID awareness is down, COVID diagnosis is late, and treatment for COVID is late | 3 | 6.52 |
| *Program Pengendalian Resistensi Antimikroba* (PPRA) approval is late/no approval, an application for antibiotics has been made | 2 | 4.35 |
| No worsening (sepsis) is expected from the start | 2 | 4.35 |
| The patient can not receive HFNC | 2 | 4.35 |
| The patient did not have an NGT installed | 2 | 4.35 |
| The patient is not transportable when going to HD | 2 | 4.35 |
| Not getting optimal therapy because of contraindications (not getting anticoagulants because there is hematemesis, not CRRT because UC is bad) | 2 | 4.35 |
| Too late to consult another specialist in the ICU | 1 | 2.17 |
| The HD procedure was delayed because the CDL device was installed 7 hours before death. | 1 | 2.17 |
| Delayed treatment decisions in the emergency room (within the first 6 hours) | 1 | 2.17 |
| The patient was not consulted for bronchoscopy after hemoptysis | 1 | 2.17 |
| Quick deterioration, no time for intubation | 1 | 2.17 |
| Cito radiation is not prepared | 1 | 2.17 |

Table 5. Suggestions for improving clinical management

| Suggestions for improving clinical management | n |
|---|---|
| Evaluation of the supervision/monitoring system during maintenance, including recording and reporting | 13 |
| Initial COVID-19 antigen examination | 5 |
| The need to provide special services for COVID-19 patients (bronchoscopy, PCI, HD, radiotherapy) | 4 |
| Increased number of HFNC | 3 |
| It is necessary to discuss serious/emergency cases with the multidisciplinary team (DPJP, PPRA and related parties) regularly | 3 |
| Giving antivirals with antigen results without waiting for PCR | 3 |
| Faster antibiotic escalation | 2 |
| Procurement of special medicines for severe/critical cases such as albumin, gamaras, tocilizumab | 2 |
| Have a referral system to other hospitals if the ICU is full | 1 |
| Emergency triage assessment in cases of severe desaturation, immediately consult the ICU | 1 |
| Cito bronchoscopy in asphyxia patients | 1 |
| Better HD timing evaluation | 1 |
| Covid PCR screening results must be faster | 1 |
| Intubation in the ER in CITO cases without waiting for the DPJP's answer | 1 |
| Maintain COVID awareness | 1 |
| Periodic Laboratory and radiology examination | 1 |
| Patients can still enter the ICU/HCU for close monitoring | 1 |
| Preparation of Bronchiectasis Clinical Practical Guideline (PPK) | 1 |
| Minimally non-invasive examination for cases with a history of post-chemo malignancy | 1 |
| Increasing awareness of pulmonary embolism cases in chronic diseases | 1 |

Table 6. Proposed improvements to managerial aspects

| Proposed improvements to managerial aspects | n |
|---|---|
| There is a need to create and evaluate special SOPs for COVID-19 with comorbid conditions, such as HD CITO SOP, radiotherapy SOP for COVID, aspiration SOP for COVID, COVID referral SOP if the ICU is full, etc | 13 |
| Additional facilities for COVID-19 patients, such as HD, monitoring equipment, portable radiology, portable ventilators are in both isolation rooms, the ICU and the emergency room | 9 |
| Increase ICU bed capacity and ICU human resources | 6 |
| Addition of special rooms for additional services specifically for COVID-19, such as radiotherapy rooms, operating rooms, cathlabs, chemotherapy rooms, resuscitation isolation room | 6 |
| Improved EWS training and implementation systems | 3 |
| The multidisciplinary team (Pulmonologist - Internal Medicine - Cardiologist) handles emergencies and intensive care in the ER | 3 |
| Training improved nursing skills | 2 |
| EWS automation system in computer/EMR | 1 |
| Have a handover checklist when moving rooms | 1 |
| There is a provision for antivirals other than favipiravir | 1 |
| Flow and placement of ER patients according to EWS | 1 |
| A medical audit was carried out | 1 |
| Evaluation of the transport of patients with HFNC from the ER to the HD | 1 |
| Case manager for comorbidities and acute infections | 1 |
| Accelerate Approval of Stent Applications | 1 |
| Optimization/monitoring and evaluation of SPO patient monitoring/supervision | 1 |
| Separation of patients with acute infections | 1 |
| Stepdown patient management (ICU -> stepdown) | 1 |
| Increased monitoring of infectious/isolated Eds | 1 |
| Increase isolation resuscitation rooms | 1 |

Meanwhile, the most proposed improvement for hospital managerial aspects is the need to create and evaluate special operation procedures standard (SOPs) for COVID-19 with comorbid conditions, such as HD CITO SOP, radiotherapy COP for COVID, aspiration SOP for COVID, COVID referral SOP if the ICU is full, etc. with 13 DPJPs. Next is the addition of facilities for COVID-19 patients, such as HD, monitoring equipment, portable radiology, portable ventilators, both in the isolation room and ICU, as well as 9 DPJP emergency rooms. Increasing ICU bed capacity and human resources is proposed by the 6 DPJP.

The next is the addition of special rooms for additional services specifically for COVID-19, such as radiotherapy rooms, operating rooms, cathlabs, and chemotherapy rooms, totaling 5 DPJPs. One of the important suggestions is improving training and the EWS implementation system, proposed by 2 DPJPs.

## DISCUSSION

From the research results, it was found that the proportion of COVID-19 variant Omicron patients who died while being treated at Persahabatan Hospital was 130/568 (22.89%). The research results show a higher proportion of deaths compared to several studies abroad. Research in South Africa found 9,555 deaths from 492,181 cases of COVID-19 infection in the Omicron predominance period. Data from South Africa shows the death ratio for the Omicron variant is 1.9%.[6] Research in the United States involving 12,936 patients with the Omicron variant of COVID-19 reported that 563 died within 14 days of testing positive for COVID-19 (mortality rate of 4.35%).[7]

The much higher proportion of deaths from the Omicron variant at Persahabatan Hospital could be due to the fact that the COVID-19 variant Omicron patients being treated were referral patients from various hospitals. Persahabatan Hospital, as a COVID-19 Referral Hospital, is prioritized for severe and critical COVID-19 patients.[8] Research data in Indonesia shows that the severity of the disease is very strongly related to the mortality of COVID-19 patients treated in hospital.[9]

Based on the demographic characteristics of the subjects in this study, the majority of subjects were male (67.7%) and aged over 60 years (54.3%). This is in line with previous studies, such as an autopsy study in Germany, which found a male predominance of 699 out of 1094 (63.9%) and most were aged 50-80 years.[10] Studies in India also show something similar, with 73% of the sample being men and the median age of death being 64 years and a range of 4-97 years.[11] Studies in Ireland obtained balanced gender proportions (50% men and 50% women) but with a much higher prevalence of ages over 60 years, namely 93.3% of the total sample.[12]

In this study, it was found that the highest nutritional status was in subjects who were overweight & obese, namely

45.7%, and as many as 14.2% were underweight. Other studies regarding death audits in COVID-19 have not recorded nutritional status in cases of COVID-19 deaths, but White et al included obesity and nutritional status among case comorbidities, with a prevalence of 13.3%.[12]

It is known that excessive nutritional status is also a risk factor for infection and more severe symptoms of COVID-19 and death. As in other studies that did not involve COVID-19 mortality audits, it was found that patients with excess body weight had a higher risk of death (HR=2.13; P=0.038) compared with patients with normal body weight.[13]

The majority (41.7%) of the subjects in this study were known to have never undergone vaccination. Incomplete vaccination status is known to be a risk factor for death in cases of the Omicron variant of COVID-19, as stated by several previous studies.[7,14] Several previous studies regarding COVID-19 death audits did not include vaccination status in their research, due to the longer data collection period in the period before COVID-19 vaccination was intensified, so that vaccination data was quite small/non-existent.[10,11]

Another study found that cases of COVID-19 deaths with unvaccinated status were only 10% of the sample, but incomplete vaccination status (only 1 time) was the majority (63.3%), which could also be due to the fact that almost the entire population in the study was elderly. which is the main target of the COVID-19 vaccination.[12]

Comorbidities such as diabetes mellitus, cardiovascular disease, and kidney disease are also known to be significant risk factors for death in the Omicron variant of COVID-19.[7,14] In this study, the most common comorbidities found were hypertension (43.3%), diabetes mellitus (37%), kidney disease (32.3%), heart disease (23.6%), and cancer (18.9%).

That is similar to the results of an audit study of COVID-19 deaths in India, where the most comorbidities from 2000 deaths were diabetes mellitus (66%), hypertension (54%), coronary artery disease (18%), and chronic kidney disease (15 %).[11] While the study in Ireland found that the most comorbidities were chronic respiratory disease (33.3%) and coronary artery disease (33.3%), followed by diabetes (23.3%), chronic neurological conditions (16.7%) and kidney disease. chronic (15%).[12]

In this study, the majority (40.9%) of patients were referred to Persahabatan Hospital in critical condition with COVID-19 and 51.2% of patients were treated in the ICU. Another study found a smaller proportion of treatment in the ICU, namely 28.3%.[12] But there has been no COVID-19 death audit study that includes the severity of COVID-19 at the time of initial admission. Another study that did not involve an audit of COVID-19 deaths stated that more severe degrees of COVID-19 and receiving invasive ventilation in intensive care had a higher risk of death (OR=3.32;

95% CI=2.01–5.48; P<0.001) compared to others.[15]

The majority (89.8%) of subjects in this study were treated for a period of <14 days until they died at Persahabatan Hospital. This critical level of COVID-19 and intensive care is in line with the short duration of hospitalization due to poor initial conditions, as also stated by studies in India, which found that the median period between the start of treatment and being declared dead in hospital was only around 2.8 to 3.6 days.[11]

This research analyzed death audits on 127 cases of deaths related to the Omicron variant of COVID-19 at Persahabatan Hospital. Based on the death audit of the entire sample, it was found that the three most common immediate causes of death were respiratory failure (38.58%), multiple organ failure/MOF (25.98%) and septic shock (16.54%). A multicenter autopsy-based study in German found that the immediate cause of death in deaths related to COVID-19 in that country was diffuse alveolar damage (DAD)/acute respiratory distress syndrome (ARDS). which covers 52.5% of all death case data found, followed by MOF at 18%.[10]

Another study based on public data in India stated that ARDS due to pneumonia was the most reported immediate cause of death, accounting for 54% of all reported deaths.[11] Meanwhile, in the pediatric population in India, the most reported causes of death are septic shock (21%), COVID pneumonia/ARDS (19%) and neonatal disease (17%), consisting of prematurity and related complications.[16]

The immediate cause of death is a condition/disease that directly causes the patient's death.[17] In this study, respiratory failure was the most direct cause of death in Omicron COVID-19 patients based on death audits, while in other studies, ARDS was the most common cause. Respiratory failure associated with COVID-19 can be included in ARDS according to the Berlin definition, but in practice, the clinical presentation of COVID-19 is different from typical ARDS.[18]

In addition to the diffuse alveolar injury typical of ARDS, respiratory failure in COVID-19 also has pathological features of endothelial injury, extensive microthrombi, and pulmonary capillary hyperplasia and has a heterogeneous clinical presentation of progressive respiratory distress and "silent hypoxemia". This difference between acute respiratory failure associated with COVID-19 and typical ARDS has given rise to much debate as to whether pneumonia due to COVID-19 is considered ARDS or not.[18] This may explain the differences between the direct causes of death reported in this study and previous studies of death audits.

Apart from that, the difference in results could also be due to differences in methods, whether an autopsy was carried out or not, as well as differences in research time, which could cause differences in the COVID-19 variant between Omicron or other variants that dominated in the time period before this research was conducted. On the other hand, multiorgan failure and septic shock were also frequently found as direct causes

of death in this study, in line with reports in previous studies.[10,16]

This research found that the three underlying causes of death were confirmed COVID-19 (42.52%), bacterial pneumonia (18.90%) and lung tumors/cancer (12.59%). These findings are quite consistent with several previous studies regarding death audits in COVID-19. The most common underlying/primary cause of death reported by autopsy-based studies in German was COVID-19 at 86.2%, while the other 13.8% was non-COVID-19, consisting of circulatory disorders (7.5%), respiratory disorders (0.9%), and others (5.4%).[10]

A prospective audit study in Ireland found that COVID-19 was the underlying cause of death in the majority (72.7%) of COVID-19-related deaths reported to the country's national surveillance system.[12] Quite different things were reported by a study in Sweden, which reported that although as many as 84% of cases of death related to COVID-19 were reported to have the underlying cause of death being COVID-19; the results of the clinical audit process were that COVID-19 was the underlying cause of death in only around 29% of cases, while the other 24% were not even related to COVID-19.[19]

The death process involves a series of events from the underlying cause of death to the immediate cause of death, which can be mediated by one/two conditions/diseases called indirect causes of death or intermediate causes of death. In this study, several causes of death were found, including sepsis (8.7-33.7%), COVID-19 pneumonia (18.9%), ARDS (11.2%), and myocarditis/myocardial injury COVID-19. As many as 19 (7.87%), which could be one of two conditions that mediate the underlying cause of death and the immediate cause of death.

There are no previous studies regarding COVID-19 death audits that clearly describe the various intermediate causes of death, but there is a study that mentions COVID-19 as an indirect cause of death in 71% of deaths related to COVID-19 in Sweden,[19] being a contributing factor to death in 21.8% of COVID-19 related deaths in Ireland,[12] as well as being a comorbidity in 13.8% of COVID-19 related deaths undergoing autopsy in German.[10]

This research found that although the majority of deaths in COVID-19 patients were deaths that could not be avoided (not avoidable), there were 25 cases (19.7%) of deaths that could have been avoided (avoidable) but occurred due to late detection of the cause of death or inadequate/optimal management given to the patient. Late detection of the cause of death is related to a lack of awareness of patient deterioration or the COVID-19 infection itself, differences in EWS writing and clinical conditions, and less than optimal supervision of patients due to limited conditions.

Delays in getting optimal service (from the regular ward to the intensive care ward) for inpatients whose clinical condition is deteriorating but which are not recognized by health workers are still common in the current era of inpatient medicine and are associated with

increased mortality rates at the hospital. A study at a tertiary teaching hospital in the United States found that as many as 64.6% of patients were transferred to the ICU facility more than 4 hours later than when they should have experienced clinical deterioration. The study also found that the mortality rate increased significantly in the 12 hours from clinical deterioration to transfer to the ICU.[20]

Early Warning Score is an approach to recognizing acute physiological deterioration in patients early, which allows the initiation of escalation of care services for patients and/or calling a rapid response medical team to provide further management. EWS can speed up the detection of deterioration and reduce mortality rates in hospitals, but sometimes there are several obstacles, such as errors in determining clinical indicators, patient variability, or individual factors of the health workers on duty, which cause its implementation to be ineffective.[21]

Meanwhile, inadequate management is related to not getting optimal treatment (including getting a place in the ICU), serious/critical medical conditions and to lack of facilities or other technical problems. Limited intensive care facilities have also been a big problem in various other studies.

A study in Uganda found that as many as 75% of treated COVID-19 patients required intensive care (experiencing oxygen desaturation or severe respiratory distress and requiring mechanical ventilation), but only 48% were able to get to the ICU. Of patients who do not receive mechanical ventilation, as many as 27% do not receive it because there is no ventilator or ICU space in the health facility where they are treated. Furthermore, the study also stated that of 71 patients with deaths that could have been avoided, 51% of deaths could have been prevented if there were empty rooms in the ICU and 33% could have been prevented if the patient had received treatment earlier.[22]

This problem of limited space has a huge impact on the health system and the death rate that occurs, especially when there is a spike in COVID-19 cases. Negative binomial regression modeling carried out by the Cybersecurity & Infrastructure Security Agency (CISA) COVID Task Force in the United States in the period July 2020-July 2021 estimates that if national ICU bed use reaches 75% capacity, there will be 12,000 additional deaths nationally in 2 weeks. If ICU bed use exceeds 100%, the additional death rate nationally is estimated at 80,000 in the next 2 weeks.[23]

A study that analyzed the results of death audits from 41 hospitals in Limpopo, South Africa, found that there were at least four important aspects that were factors related to the mortality of COVID-19 patients hospitalized in hospitals. First, provision of medical services in the emergency department is below standard, such as delays in triage & laboratory results, less than optimal monitoring & resuscitation of COVID-19 patients. Second, delayed access to health services due to an inefficient referral system,

therefore, patients come with serious/ critical conditions and complications.[24]

Third, advanced age of patients with known and unknown comorbidities, such as respiratory complications, diabetes mellitus and diabetic ketoacidosis. And last, poor case management, medical records, and medical resources and equipment related to COVID-19 (lack/exhaustion of essential medicines, undocumented medical records, staff shortages, etc.).[24]

This study compares the causes of death listed in the SMPK with the results of the death audit. It was found that the correspondence between the causes of death between SMPK and the death audit of COVID-19 patients at Persahabatan Hospital during 2022 was still quite low, namely only 23.62% for direct causes of death; 14.96% for indirect causes of death (intermediate causes of death); and 51.97% for the basic cause of death.

A study in Sweden also found that the conformity in writing the cause of death between the death certificate and the death audit by the research team was still quite low. Based on data on death certificates obtained from the Swedish National Board of Health and Welfare, COVID-19 was the underlying cause of death in 84% of cases and an indirect cause of death in 16% of cases; Meanwhile, based on the results of an audit conducted, it was found that COVID-19 was only the basic cause of death in 29% of cases, was an indirect cause of death in 71% of cases, and was not related to 24% of other deaths.[19]

A study that analyzed autopsy results on 65 cases of death related to COVID-19 in Cuba also found that there was a discrepancy between the cause of death determined from the autopsy and that written on the medical death certificate. In cases related to COVID-19, the discrepancy rate reached 19.4% for the basic cause of death and 64.5% for the direct cause of death.[25]

Further analysis of the factors that influence the differences in causes of death between SMPK and death audits needs to be carried out to reduce existing discrepancies. Inconsistencies in filling out the SMPK can be caused by problems with the patient's condition, administration, differences in definitions of causes of death, and staff compliance with operational standards.[3]

The various problems that can be identified as root causes of avoidable causes of COVID-19 deaths in this research deserve special attention so that they can be corrected to reduce the death rate in the future. This is in line with the stages in a death audit, namely making efforts to correct the deficiencies that have been identified and then carrying out a re-evaluation to determine the impact of whether there is a reduction in the death rate that can be prevented after making improvements.[26]

Systemic and collaborative efforts are needed to make improvements related to problems identified from audit results. Based on the results of the interview, there were various inputs from the DPJP regarding service improvements at

Persahabatan Hospital, which can be grouped into clinical patient management aspects and hospital managerial aspects.

Improvements to aspects of clinical patient management proposed by DPJP include evaluation of the patient supervision/monitoring system; COVID-19 antigen examination to detect COVID-19 more quickly; increase in the number of HFNC in hospitals; providing special services for COVID-19 patients (bronchoscopy, PCI, HD) as well as discussing serious/emergency cases with the multidisciplinary team. Meanwhile, improvements to hospital managerial aspects include creating and evaluating special operation procedures standard (SOPs) for COVID-19 with comorbid conditions; as well as adding facilities, capacity, human resources and space for additional services specifically for COVID-19 patients.

Evaluation of the patient supervision/monitoring system can be carried out through education and training for clinicians and teams related to patient care so that they have sufficient knowledge regarding EWS and patient deterioration; can respond responsibly; follow protocols well; and can provide ongoing support to advocate for service improvements and activate *tim medis reaksi cepat* (TMRC) if necessary.[21]

Innovations such as the use of technology in the form of wireless devices worn on patients can enable continuous monitoring of vital signs & signs of clinical deterioration of patients which is useful in reducing TMRC activation by up to 53%, strengthening decision-making steps for 74% of nurses, and reducing length of stay in the ICU from 2.82 days to 2.19 days.[27] The strategy of implementing the COVID-19 antigen test on patients, which is faster and cheaper than RT-PCR, also has the benefit of reducing patient isolation time to 144 hours so that patients can also receive appropriate treatment more quickly.[28]

Increasing the capacity of medical facilities and equipment needed by COVID-19 patients has become a global response to the increasing need for these facilities at the peak of the wave of COVID-19 cases. ICU facilities across Australia have succeeded in increasing bed capacity to 191% of the initial number and increasing invasive ventilation to 120% of the initial number in response to increasing needs during the COVID-19 pandemic.[29] With the increase in hospital facilities, it is hoped that more severe to critical COVID-19 patients will be able to receive optimal treatment.

Apart from that, many COVID-19 patients also have comorbidities and require special treatment such as hemodialysis, percutaneous coronary intervention (PCI) and bronchoscopy. Restrictions on these services are often carried out as an effort to guard against the spread of COVID-19 infection, so that additional special isolation places are needed along with special standard operating procedures so that COVID-19 patients can still receive health services according to their medical condition with minimal risk of virus transmission.

The success of the strategy for creating special facilities and protocols for COVID-19, for example, in one of the hemodialysis services in London, is that the hemodialysis unit that implemented this special strategy had a lower number of COVID-19 cases and deaths due to infection compared to units in other areas of London.[30] Another study in Italy that implemented a special protocol for acute coronary syndrome patients with COVID-19 infection stated that carrying out emergency PCI according to a special protocol improved the prognosis for all patients except for patients with the most severe medical conditions.[20]

Efforts to improve facilities and special operational standards can be replicated in other units, accompanied by increasing human resource capacity in order to reduce the death rate due to/with COVID-19, as per the results of the death audit in this study.

## CONCLUSION

From the death audit analysis carried out and the discussion of this research, it can be concluded that the proportion of COVID-19 variant Omicron patients who died while being treated at Persahabatan Hospital was 22.89%. The three most common direct causes of death are respiratory failure, multiple organ failure (MOF) and septic shock. Meanwhile, the 3 (three) basic causes of death were confirmed COVID-19 at 42.52%, bacterial pneumonia at 24 cases at 18.90% and tumor/lung cancer at 12.59%.

As many as 42.52% of the Omicron variant COVID-19 patients who died during 2022 were due to COVID-19 and 57.48% were due to COVID-19. There are 25 cases of avoidable COVID-19 variant Omicron deaths. The root of the problem of late detection of the cause of death is a lack of alertness, so that it does not predict worsening, EWS assessments that are not clinically appropriate, and late detection of COVID infection due to decreased alertness.

Meanwhile, the 3 biggest roots of inadequate management problems are that the hospital ICU room is full, patients are in end-stage or "do not resuscitate" (DNR) condition, so that the ICU is not as much of a priority and the facilities for special management of patients with COVID-19 are less than optimal. In assessing the suitability of the causes of death listed in the SMPK with the results of the death audit, only 23.62% corresponded to the direct cause of death, and 51.97% were appropriate for the underlying cause of death.

There are 3 most significant suggestions for improving clinical management, namely evaluating the patient supervision/monitoring system, testing for COVID-19 antigens carried out earlier before polymerase chain reaction (PCR), and providing special services for patients with COVID-19 with comorbidities. Meanwhile, the top 3 suggestions for improving hospital managerial aspects are the need to create and evaluate a special SOP for COVID-19 with comorbid conditions, adding special service facilities

for COVID-19 patients with comorbidities and increasing ICU bed capacity and human resources.

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Original Article

# Air Quality and Correlation of Exhaled Carbon Monoxide Level with Lung Function among Petrol Station Attendants in Banda Aceh

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## Abstract

**Background:** Risks of developing respiratory diseases due to pollutant exposures at petrol stations are high. The pollutants, such as particulate matter, carbon monoxide (CO), and volatile organic compounds emitted from vehicle exhaust and gasoline vapours, may affect the lung function of petrol station attendants. This study aimed to assess the levels of particulate matter, total volatile organic compounds, and the correlation of CO level and lung function among petrol station attendants in Banda Aceh.

**Method:** An analytical observational study with a cross-sectional design involved 114 attendants from 12 petrol stations in Banda Aceh. Lung function was evaluated using spirometry, and CO exhalation levels were measured using a Smokerlyzer. In addition, particulate matter and total volatile organic compounds levels were measured in the petrol station area using an air quality monitor.

**Results:** Most participants were male (82.5%) with a mean age of 30 years. The duration of work was under 5 years in 68 participants (59.6%). Approximately 61.4% (70 samples) were active smokers, with the most common Brinkman index indicating mild smoking habits for 50 samples (43.9%). The Pearson chi-square test revealed no significant relationship between CO exhalation levels and decreased lung function (P=0.118). The level of TVOC exceeded safe limits at all gas stations (>0.601 mg/m$^3$), with an average TVOC level of 7.53 mg/m$^3$. Most participants showed above-normal expiratory CO levels (53.6%). The average of the PM2.5 level was moderate.

**Conclusion:** This study found no significant correlation between exhaled CO levels and decreased lung function among petrol station attendants, likely due to their shorter duration of work and age under 40 years.

**Keywords:** exhaled CO, lung function, particulate matter, petrol station, volatile organic compound

## INTRODUCTION

Environmental pollution has been a global issue for decades. Various causes of air pollution include increasing industrialization, rising energy demands, and the growing number of vehicles traversing the streets daily. To address these needs, there has been a surge in the

construction of public fuel filling stations.[1,2] Gas stations, however, pose numerous risks and threats to both employees and the environment.[2–4]

Air pollutants emanating from vehicle exhaust, such as Particulate Matter (PM), carbon monoxide (CO), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), ozone ($O_3$) and benzene, classified as Volatile Organic Compounds (VOCs) or volatile substances, play a role in the pathogenesis of respiratory diseases.[1,2,4]

Inhalation of CO is considered potentially toxic to the body, resulting in a decrease in the ability to transport oxygen, as indicated by elevated carboxyhaemoglobin (COHb) levels. Jadoon et al demonstrated that high carbon monoxide saturation in the blood is associated with several diseases. Breathing problems are the most commonly reported issues.[5]

Gasoline is categorized within the VOC group due to its volatile nature. The concentration of gasoline vapor in the atmosphere (approximately 2000 parts per million) poses a risk when inhaled, even for short periods (seconds). In their research, Temam et al revealed a significant decrease in FVC, $FEV_1$, $\%FEV_1$, and $FEF_{25-75\%}$ among the study group (petrol station operators) compared to the control group.[2] PM2.5 air pollution levels in Indonesia are a good level in 0-15 $\mu g/m^3$, a moderate level in 16-65 $\mu g/m^3$, unhealthy in 66-150 $\mu g/m^3$, very unhealthy in 151-250 $\mu g/m^3$, and a hazardous level in >250 $\mu g/m^3$.[1–4]

The purpose of this study is to determine the levels of PM, total VOC (TVOC), and the relationship between carbon monoxide exhalation and the lung function of petrol station operators in Banda Aceh.

## METHOD

This study adopts an observational research design with cross-sectional approaches to analyze PM and TVOC at gas stations in Banda Aceh and has received ethical approval from the Research Ethics Committee of Zainoel Abidin Hospital with the approval number 070/ETIK-RSUDZA/2023. Additionally, it aims to investigate the influence of CO on operators' lung function. The population under consideration comprises all petrol station operators in Banda Aceh.

Inclusion criteria for participant selection encompass operators who willingly consent to be part of the study and petrol station operators with a work experience of ≥1 year who have no history of comorbid pulmonary disease. Exclusion criteria involve operators contraindicated for spirometry.

The primary data for this study is derived from the assessment of lung function utilizing spirometry, measurement of expiratory carbon monoxide using Smokelyzer, TVOC measurement using the Ambient Air Quality Pollution Meter (AQM-01), and basic demographic information from a questionnaire.

The procedure is carried out at the end of the worker's shift to assess lung function utilizing spirometry, measurement of expiratory carbon monoxide using a

smokerlyzer, TVOC measurement using the Ambient Air Quality Pollution Meter (AQM-01), and basic demographic information from a questionnaire. This study has been ethically approved using humans as research subjects and approved by Syiah Kuala University.

Data analysis is conducted using the Statistical Package for the Social Sciences (SPSS). Univariate analysis is employed to examine frequency distribution, proportion of variables, and sample characteristics. Bivariate analysis is utilized to explore the association between expiratory carbon monoxide levels and lung function. The chi-square test is applied for bivariate analysis, where P>0.05 indicates no significant association between the two variables.

## RESULT

A total of 114 samples met the inclusion criteria for this study. However, three samples were excluded due to a working period of less than one year or a history of asthma. Table 1 shows the characteristics of the subjects.

Regarding smoking habits, the majority of subjects were active smokers (70 samples; 61.4%), with the most common Brinkman index (BI) falling into the mild category (50 samples; 43.9%). Approximately 61.4% of subjects exhibited normal nutritional status. Body mass index (BMI) classification was based on national standards.

The use of masks was prevalent among subjects, with 91 subjects (79.8%) reporting regular use. The majority of samples had a length of service ranging from 1 to 5 years (68 samples; 59.6%).

Table 1. General characteristics of subjects

| Characteristic | n | % |
|---|---|---|
| Gender | | |
| Male | 94 | 82.5 |
| Female | 20 | 17.5 |
| Age (years) | | |
| 18-25 years | 48 | 42.1 |
| 26-35 years | 42 | 36.8 |
| 36-45 years | 15 | 13.2 |
| >45 years | 9 | 7.9 |
| Smoking History | | |
| Smoker | 70 | 61.4 |
| Smoked before | 9 | 7.9 |
| Non-smoker | 35 | 30.7 |
| Brinkman index | | |
| Mild | 50 | 43.9 |
| Moderate | 16 | 14.0 |
| Severe | 4 | 3.5 |
| Non-smoker | 44 | 38.6 |
| BMI | | |
| Underweight (<18.5) | 9 | 7.89 |
| Normal (18.5-25.0) | 70 | 61.4 |
| Overweight (≥25.1) | 35 | 30.7 |
| Using Mask | | |
| No | 23 | 20.2 |
| Yes | 91 | 79.8 |
| Working Time | | |
| 1-5 years | 68 | 59.6 |
| 6-10 years | 40 | 35.1 |
| >10 years | 6 | 5.3 |

Out of the 12 gas stations studied, 2 had PM2.5 levels classified as good, 9 had the moderate category, and only 1 had the unhealthy category, exceeding the threshold value (68 µg/m$^3$) (Table 2).

Table 2. Particulate Matter 2.5 µm TVOC levels in a petrol station at Banda Aceh (n=12)

| PM2.5 | n | % |
|---|---|---|
| Good | 2 | 16.7 |
| Moderate | 9 | 75 |
| Unhealthy | 1 | 8.3 |
| Very unhealthy | 0 | 0.0 |
| Hazardous | 0 | 0.0 |

Table 3. Total Volatile Organic Compound (TVOC) levels at Banda Aceh gas stations (n=12)

| TVOC | n | % |
|---|---|---|
| Below the safe threshold | 0 | 0 |
| Above the safe threshold | 12 | 100 |

The TVOC levels were found to be above the safe threshold (>0.601 mg/m$^3$) at all gas stations studied, as shown in Table 3.

Table 4. Expiratory carbon monoxide (CO) levels and lung function of petrol station operators at Banda Aceh gas stations (n=114)

| Indicators | n | % |
|---|---|---|
| Expiratory CO Category | | |
| Normal (0-6 ppm) | 53 | 46.5 |
| Mild (7-10 ppm) | 15 | 13.2 |
| High (≥11 ppm) | 46 | 40.4 |
| Lung Function | | |
| Normal | 89 | 78.1 |
| Obstruction | 3 | 2.6 |
| Restriction | 21 | 18.4 |
| Mixed | 1 | 0.9 |

Expiratory CO levels were above normal in the majority of samples, with 15 subjects (13.2%) mildly increased and 46 subjects (40.4%) highly increased. A significant proportion of subjects exhibited normal lung function (78.1%), with lung function disorders predominantly characterized by restriction abnormalities (18.4%), as shown in Table 4.

Table 5. The correlation between expiratory carbon monoxide levels and lung function at petrol station operators in Banda Aceh (n=114)

| Expiratory CO | Lung Function | | Total | P |
|---|---|---|---|---|
| | Normal | Abnormal | | |
| Normal | 43 (81.1%) | 10 (18.9%) | 53 (100.0%) | 0.118 |
| Mild | 14 (93.3%) | 1 (6.7%) | 15 (100.0%) | |
| High | 32 (69.6%) | 14 (30.4%) | 46 (100.0%) | |
| Total | 89 (78.1%) | 25 (21.9%) | 114 (100.0%) | |

However, the analysis revealed no significant relationship between expiratory carbon monoxide levels and the lung function of petrol station operators in Banda Aceh (P=0.118), as shown in Table 5.

## DISCUSSION

This study, involving 114 petrol station operators in Banda Aceh, aimed to analyze levels of PM, TVOC and determine the correlation between exhaled carbon monoxide and the lung function of petrol station operators across 12 gas stations. The research found that 2 gas stations had PM2.5 levels in the good category, while had levels in the medium category (16-65 µg/m$^3$, still below the threshold, and only 1 petrol station had PM levels in the unsafe category.

These findings contrast slightly with Ramadhany et al's research in Jakarta, where all research locations had PM2.5 levels in the safe category.[3] The difference may be attributed to the location of gas stations in Banda Aceh, primarily situated on provincial roads congested with vehicles, unlike the predominantly district road locations in Jakarta.

PM2.5 is generated not only by vehicles queuing for refuelling, but also by dust and fumes from vehicles traversing the highway. With an aerodynamic diameter of 2.5 µm or less, PM2.5 contains various toxic chemicals that can penetrate deep into the peripheral respiratory tract, posing a significant health risk, for example, decreased lung function, an

accelerated annual decline in lung function, and an increased risk of developing chronic obstructive pulmonary disease (COPD).[3,6]

The measurement of TVOC levels at all gas stations indicated unsafe levels (>0.601 mg/m$^3$). Comparisons with research conducted by Salama et al on the concentration levels of benzene, toluene, and xylenes (BTX) around gas stations showed levels exceeding air quality standards.[7] Similarly, studies in Japan and Sudan found elevated VOC levels around gas stations.[8,9]

Gasoline, diesel, and burning fossil fuels are primary sources of benzene-containing VOCs. Numerous studies have investigated the association between benzene exposure and decreased lung function, with evidence pointing towards an increased risk of impaired lung function in exposed workers.[10,11]

Recent research has revealed inflammatory and oxidative imbalances that influence the expression of genes directly involved in hyperresponsiveness, airway hyperplasia, and airway remodelling in both atopic and nonatopic subjects.[10,11] Personal protective equipment, including standard masks, becomes crucial in minimizing VOC exposure to the respiratory tract.[12]

From our research, a substantial number of subjects exhibited abnormal expiratory CO levels, with 15 subjects (13.2%) having mild levels (7-10 ppm) and approximately 46 subjects (40.4%) having high levels (≥11 ppm). These findings align with research by Ana et al, which demonstrated significantly higher average COHb levels in petrol station attendants compared to WHO guidelines.[13]

A study by Okeke and Kelechi comparing COHB levels among smokers, petrol station attendants, and control subjects found that COHb was significantly higher in smokers than in petrol station attendants and the control group. Continuous exposure to carbon monoxide from vehicle exhaust fumes can contribute to increased exhaled carbon monoxide levels in petrol station attendants.[14]

This aligns with previous research in Salatiga, which established a strong correlation between COPD patients' levels of obstruction and smoking severity.[15] Education on the significance of quitting smoking is crucial to reduce exposure to CO gas for petrol station operators who are also active smokers.

Exhaled carbon monoxide measurement in this study utilized a CO detector (Smokelyzer), offering a non-invasive and cost-effective means of assessing CO levels in breath.CO concentrations vary with distance from traffic, and concentrations near motorized vehicles can be 2-5 times higher than in the surrounding air. Gasoline, a major source of CO, produces elevated levels in exhaust fumes, particularly if the engine is not working correctly. This underscores the importance of monitoring CO levels, especially for petrol station attendants.[16]

The majority of samples in this study exhibited normal lung function (78.0%), influenced by the characteristics such as a predominantly male sample, the age range of 18-25 years (a period of maximum lung

development), and a higher proportion of smokers with a mild Brinkman index. BMI and working period also play roles in lung function. Underweight individuals may experience decreased respiratory muscle strength, while excess body weight can burden the thorax and abdomen, reducing lung volume.[15,17,18]

The working period, especially over 5 years, is associated with decreased lung function, emphasizing the cumulative impact of long-term exposure to pollutants. A study by Novtasari et al demonstrated that workers with work periods ≥5 years exhibit 8.3 times greater risk of developing abnormal pulmonary function compared to someone who has worked <5 years. These results are consistent with the theory that individuals working in environments with high levels of pollutants over an extended period are at risk of decreased lung function.[19,20]

In this study, lung function disorders were primarily characterized by restriction disorders (18.4%). This aligns with previous studies conducted on petrol station attendants, indicating that most observed lung function disorders were restrictive. Restriction refers to a disturbance in lung expansion for any reason, resulting in stiffened lungs, increased force for expansion, and subsequent chest wall shrinkage.[1,3,15]

The study also measured spirometry results, including Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second ($FEV_1$), $FEV_1$/FVC, %FVC, and %$FEV_1$. The average FVC value of the 114 research subjects was 3065.43 ml with a standard deviation (SD) of 471 ml. The mean value of $FEV_1$ was 2719.64±465 ml, and the mean %FVC was 87.03±10.38%. The average %$FEV_1$ was 90.17±13.77%, and the average value of $FEV_1$/FVC was 99.85±11.49%.

The research results indicate that the average FVC value of 114 petrol station operators was 3065.43 ml with SD of 471 ml. The mean %FVC was 87.03±10.38%. This finding contrasts with the study by Ramadhany et al, which reported an average FVC of 2868.4±733.74 ml and an average %FVC value of 81.6±15.0%. One possible explanation for this difference is the higher proportion of male respondents in your study (82.5%) compared to the Ramadhany study.[3]

Gender differences play a significant role in lung capacity, as lung volume and capacity in women are approximately 20-25% smaller than in men. The mean value of $FEV_1$ is 2719.64±465 ml. This result is comparable to the findings of Zafar's research in Pakistan, which reported an average $FEV_1$ of 2430±890 ml.[21]

In this study, the average %$FEV_1$ was 90.17±13.77%, and the average value of $FEV_1$/FVC is 99.85±11.49%. This result is lower than those reported by Shonga and Siziya in Zambia, who found %$FEV_1$ to be 98.8±23.2% and $FEV_1$/FVC to be 110.2±12.42%.[22]

The chi-square analysis indicated that there was no significant relationship between exhaled carbon monoxide levels and the lung function of petrol station operators in Banda Aceh, with P=0.118. This finding aligns with similar results

obtained from Novtasari's research in Semarang, where no significant relationship was found between carbon monoxide exposure and lung function characteristics in petrol station attendants (P=0.720).[20]

However, the study findings differ from those of Awadallah et al in Egypt, which revealed a significant reduction in pulmonary function parameters, including $FEV_1$, FVC, PEFR, and $FEFR_{25\%-75\%}$ among petrol station workers (group II) compared with a control group (group I). Additionally, they observed a statistically significant increase in the mean value of CO in the study group (petrol station workers) compared to values in the control group (0.33±0.15).[1]

The results of the analysis by Esha et al in Riau present a significant correlation (r= -0.795) between exposure to CO pollutant gas and lung function. Prolonged exposure to CO has been associated with asthma exacerbations, chronic bronchitis (chronic obstructive pulmonary disease or COPD), and an increased susceptibility to respiratory diseases.[12]

The terminal bronchioles and respiratory bronchioles are crucial locations where emissions from vehicle exhaust, including CO, can have a significant impact. These particles, with their large surface area, can carry various toxic substances, remaining in the atmosphere for extended periods, and depositing in the small airways of the lungs.[1]

One limitation of this study is that the researchers did not personally measure the levels of particulate matter and total volatile organic compounds at each petrol station operator, aiming to avoid bias. This limitation arises from constraints related to the measuring instruments.

## CONCLUSION

In conclusion, this study reveals that the levels of $PM_{2.5}$ and TVOC in Petrol station areas exceed acceptable levels, posing potential harm. The majority of subjects in this study exhibit expiratory CO levels above the normal range, with the most prevalent lung function abnormality being restriction. To mitigate health risks associated with chronic exposure to fuel, it is recommended to implement periodic health checks and pre-work examinations. These measures include lung function assessments using spirometry, monitoring expiratory CO levels with Smokelyzer, and the use of protective masks. Additionally, encouraging smoking cessation is advised to reduce the risk of exposure to carbon monoxide.

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Case Report

# Improving Physical Endurance in Palliative Stage IV Lung Cancer: A Case Report

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## Abstract

**Background:** Lung cancer remains the leading cause of cancer-related mortality worldwide, with advanced stages often causing fatigue, reduced endurance, and impaired lung function. Pulmonary rehabilitation, including incentive spirometry exercise (ISE) and aerobic exercise, has been proven effective in improving functional capacity in patients with lung cancer, even in palliative care settings. This case report examines the effects of ISE and aerobic exercise on a stage IV lung cancer patient.

**Case:** A 58-year-old male with stage IV lung cancer and spinal metastases experienced increased fatigue, especially after walking 500 meters. He underwent a four-weeks palliative rehabilitation program that included individualized supportive exercises (ISE) and moderate aerobic activity.

**Discussion:** Following the completion of the program, the patient showed improvements in respiratory function, thoracic expansion, walking ability and overall performance status. His walking distance increased from 450 meters to 522 meters, and his MET score improved, indicating an enhancement in cardiovascular fitness. Despite a decline in forced vital capacity (FVC), other indicators show significant improvements in his physical function and quality of life.

**Conclusion:** The combination of ISE and aerobic exercise proves to be an effective rehabilitation approach in improving respiratory function, physical endurance, and quality of life with stage IV lung cancer, even within the palliative care phase.

**Keywords:** aerobic exercise, incentive spirometry, lung cancer, METs

## INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide.[1] In Indonesia, lung cancer ranks third overall, while it remains the most common cancer among males.[2] Despite advancements in treatment, patients diagnosed with lung cancer patients with survive over five years often experience a significant decline in their quality of life, with a 35% reduction in functional well-being. While managing chronic symptoms can be challenging,

approximately 15% of patients demonstrate an impressive ability to adapt, underscoring the importance of addressing their physical and emotional needs during palliative care to provide high-quality end-of-life care.[3,4]

In the advanced stages of lung cancer, patients frequently face treatment-related issues, including fatigue, reduced physical endurance, and impaired pulmonary function.[5] These factors severely impact quality of life, with over 75% of patients with metastatic disease reporting experiencing cancer-related fatigue (CRF).[6]

In addition, lung cancer patients often experience obstructive lung function, as evidenced by decreased forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC) ratio.[7] These impairments can significantly limit exercise capacity, further hindering physical activity, especially in those with moderate airflow restrictions.[8]

Given these challenges, pulmonary rehabilitation has emerged as a vital aspect of supportive care for lung cancer patients.[9] The American Thoracic Society (ATS) and the European Respiratory Society (ERS) highlight pulmonary rehabilitation as an effective method for enhancing exercise capacity and overall functional.[10] Combining pulmonary rehabilitation with aerobic exercise has been shown to yield even better outcomes, improving both physical endurance and respiratory function.[11]

Additionally, the use of incentive spirometry (IS) has demonstrated positive effects, with studies reporting a 16% increase in maximal inspiratory volume after consistent use over 30 days.[12] Other studies have shown that inspiratory muscle exercise using IS my improve lung function, especially by enhancing FVC.[13]

Physical activity provides additional benefits for cancer survivors, including reduced fatigue through enhanced cardiorespiratory fitness, improved physical performance, and elevated energy levels.[14] Furthermore, the Tokuhashi and Tomita scores are commonly used to predict a patient's survival prognosis and inform treatment decisions. These scores help determine whether a patient may benefit from more intensive treatments or if palliative care is the more appropriate approach. These scoring systems play a critical role in tailoring interventions based on individual patient needs.[15]

A crucial component in managing stage IV lung cancer patients is assessing their functional status. The Karnofsky Performance Scale (KPS) is commonly used to evaluate a patient's ability to perform daily activities and their level of dependence. This scale, ranging from 0 (dead) to 100 (normal), provides clinicians with an essential tool for tracking changes in physical status and guiding treatment decisions. As physical performance directly correlates with quality of life, performance assessment becomes a key indicator for prognosis and treatment planning.[16,17]

In this report, we present a case study of a stage IV lung cancer patient,

focusing on the combined impact of incentive spirometry exercise (ISE) and aerobic exercise on physical endurance, as demonstrated by improvements in functional respiratory capacity. This case highlights the potential benefits of rehabilitative interventions in palliative care settings, offering a tailored approach to enhancing the quality of life for patients facing advanced lung cancer.

## CASE

A 58-year-old male with a history of stage IV lung cancer presented to the hospital with a primary complaint of fatigue, particularly when walking long distances. Over the past month, the fatigue had worsened significantly, and he now experiences substantial fatigue after walking just 500 meters. Despite these symptoms, the patient denies shortness of breath, cough, or chest pain.

The patient was diagnosed with stage IV lung cancer two years ago. According to the TNM classification system, imaging revealed the following findings: A heterogeneous, solid mass with partially defined (articulated) margins is located in segment 3 of the right lung. Post-contrast imaging shows the lesion measures 2.4 × 2.5 × 1.3 cm, reduced from a previous measurement of 3.2 × 2.0 × 4.4 cm, suggesting a partial response or regression. The mass obliterates the B3B branch of the right bronchus, forming an open bronchus sign, and is in close contact with the right-sided pericardium, indicating local invasion.

These features particularly pericardial involvement and bronchial obstruction are consistent with T4 classification, which denotes a tumor of any size that invades the mediastinum, heart, great vessels, trachea, or pericardium, or involves separate tumor nodules in the same lobe, there is no enlargement or abnormal contrast enhancement is observed in the hilar or mediastinal lymph nodes. Thus, the nodal status is classified as N0.

Suspected metastatic involvement of the L2 vertebral body, as well as the body and bilateral pedicles of the L3 vertebra; these findings are interpreted as M1b, which denotes a single extrathoracic metastasis (or involvement of a single organ), in this case, the spine. Based on the above findings, the patient's lung cancer is staged as: T4-Invasion of pericardium and bronchus, N0 -No regional lymph node involvement, M1b - Suspected vertebral metastasis (L2 and L3) resulting in IVB Stage IV Lung Cancer.[18]

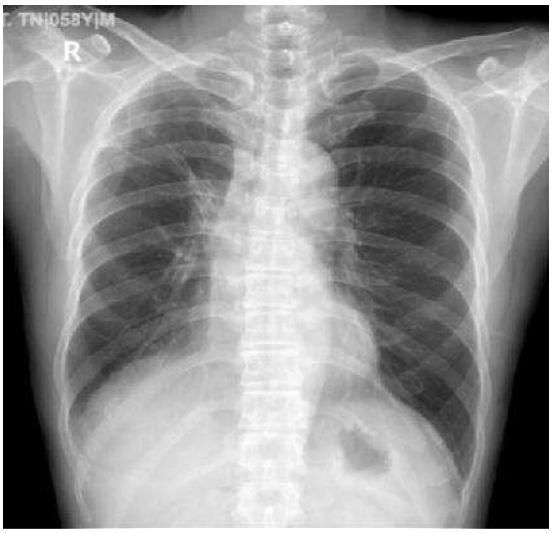

Figure 1. Chest x-ray showed heterogeneous opacities and fibrosis in the upper-middle right lung

Initial diagnostic workup included chest X-ray, which showed heterogeneous opacities and fibrosis in the upper-middle right lung fields (Figure 1).

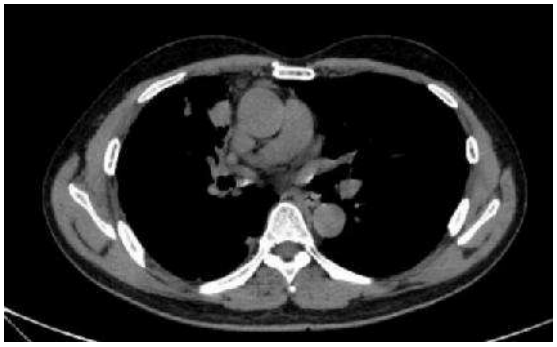

Figure 2. CT scan revealed a malignant-appearing mass in the right lung

A CT scan revealed a malignant-appearing mass in the right lung's segment 3 measuring (Figure 2). Thoracolumbar MRI further confirmed these findings, revealing sclerotic lesions in the L2-L3 vertebral bodies as well as in the right and left pedicles of L3 (Figure 3). His treatment history includes completed chemotherapy and a bone marrow replacement surgery performed on the L4 vertebra, performed one month before this visit.

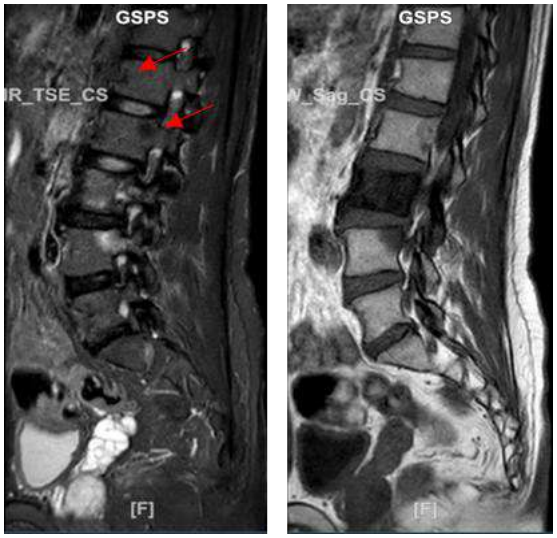


Figure 3. Thoracolumbar MRI showed sclerotic lesions in L2-L3

Physical examination findings, thoracic expansion measurements revealed decreased values at three key levels: the axillary level (1.5 cm), areola level (4 cm), and xiphoid level (2.5 cm). A spirometry test was conducted to evaluate lung function, and the results showed a forced vital capacity (FVC) of 2170 mL.

Table 1. Tokuhashi scoring system[15]

| Characteristic | Score |
|---|---|
| General Condition (performance status) | |
| Poor (PS 10%-40%) | 0 |
| Moderate (PS 50%-70%) | 1 |
| Good (PS 80%-100%) | **2** |
| Number of extraspinal bone metastases foci | |
| >3 | 0 |
| 1-2 | **1** |
| 0 | 2 |
| Number of metastases of the major organs | |
| >3 | 0 |
| 2 | **1** |
| 1 | 2 |
| Metastases to the major internal organs | |
| Unremovable | 0 |
| Removable | 1 |
| No metastases | **2** |
| Primary site of the cancer | |
| Lung, osteosarcoma, stomach, bladder, esophagus, pancreas | **0** |
| Liver, gallbladder, unidentified | 1 |
| Others | 2 |
| Kidney, uterus | 3 |
| Rectum | 4 |
| Thyroid, breast, prostate, and carcinoid tumor | 5 |
| Palsy | |
| Complete (frankel A,B) | 0 |
| Incomplete (frankel C,D) | 1 |
| None (frankel E) | **2** |
| Total Score | **8** |

These findings suggested significant lung volume impairment, which caused a decrease in oxygen capacity, thereby

contributing to his fatigue during physical activities. The patient's performance status was assessed using the KPS, which indicated a score of 60%, meaning he requires occasional assistance but can care for most of his personal needs.

A prognostic evaluation was conducted using two established scoring systems, the Tokuhashi scoring system and the Tomita scoring system, to assess the patient's life expectancy and guide subsequent treatment decisions. The Tokuhashi scoring system, which evaluates factors such as general condition, the number of bone and organ metastases, neurological status, and the type of primary tumor, resulted in a total score of 8 points (Table 1).

This score suggests a life expectancy of less than 6 months, where palliative care is recommended as the primary approach. The Tomita scoring system, which assesses prognosis based on tumor growth rate, visceral organ involvement, and bone metastases, resulted in a score of 6 points (Figure 5).

| Scoring System | | | | Prognostic Score | Treatment Goal | Surgical Strategy |
|---|---|---|---|---|---|---|
| Point | Prognostic factors: Primary tumor | Visceral mets.* | Bone mets.** | | | |
| 1 | slow growth (breast, thyroid, etc.) | | solitary or isolated | 2, 3 | Long-term local control | Wide or Marginal excision |
| 2 | moderate growth (kidney, uterus, etc.) | treatable | multiple | 4, 5 | Middle-term local control | Marginal or Intralesional excision |
| 4 | rapid growth (lung, stomach, etc.) | un-treatable | | 6, 7 | Short-term palliation | Palliative surgery |
| | | | | 8, 9, 10 | Terminal care | Supportive care |

★ No visceral mets. = 0 point. ★★ Bone mets. including spinal mets.

Figure 5. Tomita scoring system[15]

The patient's total score is 8, calculated as follows: good condition (2 points), 1-2 extraspinal bone metastases (1 point), 2 of metastases in the vertebral body (1 point), no metastases to the major internal organs (2 points), primary cancer site at the lung (0 point), and no Palsy (2 points).

The patient's prognostic score was calculated as follows: rapid growth of the primary tumor in the lung (4 points), no visceral metastases (0 points), and multiple bone metastases (2 points). The total prognostic score is 6, with the treatment goal being short-term palliation through palliative surgery.

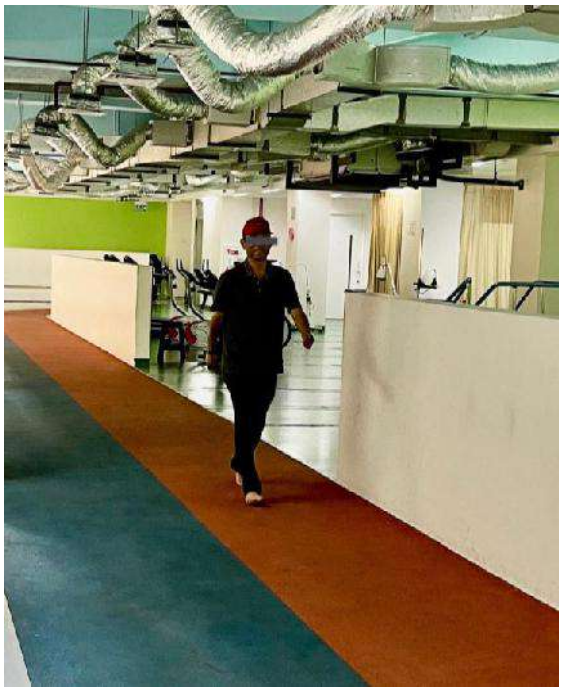

Figure 6. The 6-minute walking test (6MWT) was performed before and after the rehabilitation program

Based on these findings, the patient was enrolled in a palliative rehabilitation program, including an incentive spirometer (ISE), with instructions for the patient to perform 10 breaths three times

daily over 4 weeks. This was combined with moderate exercise, was developed using the results of a 6MWT. The 6MWT was performed before and after the rehabilitation program. There was an improvement in the walking distance from 450 to 522 meters, indicating enhanced endurance and cardiovascular fitness (Figure 6)**.**

During the test, the patient could initially walk a distance of 450 meters and had a metabolic equivalent of task (MET) score of 5.2. Based on these results, the program prescribed walking 2000 meters three times a week. This combination was tailored to improve the patient's functional capacity while taking into account his overall prognosis and physical limitations.

## DISCUSSION

Lung function improvement is crucial for enhancing comfort and quality of life in patients with end-stage lung cancer, as respiratory difficulties are common in this patient population. ISE has proven to be an effective, low-cost, and user-friendly tool that aligns with the patient's natural breathing pattern.[4,12]

Incentive spirometry encourages slow, deep breaths, which help open collapsed airways, thereby improving lung ventilation. This technique has minimal side effects, requires little supervision after training, and has been shown to significantly enhance exercise capacity and improve the quality of life in lung cancer patients, particularly those with advanced disease. In this case, the use of ISE contributed to significant functional improvements in the patient's respiratory capacity.[4,12]

The patient's prognosis was assessed using two established scoring systems: the Tokuhashi and Tomita scoring systems. The Tokuhashi score of 8 points indicated a life expectancy of less than six months, suggesting that palliative care should be prioritized. This was in alignment with the decision to enroll the patient in a palliative rehabilitation program.

The Tomita score, which emphasized the rapid growth of the primary tumor and the presence of multiple bone metastases, further reinforced the need for a palliative approach. Both scoring systems were instrumental in guiding the rehabilitation strategy, which focused on improving functional capacity and managing symptoms despite the patient's limited prognosis.

Four weeks after starting the combination program, significant improvements were observed in the patient's respiratory function and physical endurance. First, the patient's airflow during ISE increased from 600 mL/s to 900 mL/s, reflecting enhanced lung ventilation and improved breathing mechanism, helping the patient manage the respiratory demands of daily activities. This improvement in airflow demonstrates that ISE effectively targeted airway patency and lung function, which is critical for patients with advanced lung cancer and compromised pulmonary

function.

Second, thoracic expansion measurements showed significant improvement at all three levels: from 1.5-4-2.5 cm to 3-5-3.5 cm. This improvement suggests an increase in chest wall mobility, leading to enhanced lung expansion during inspiration. These improvements are important for lung cancer patients who often experience reduced chest wall mobility and ventilation, further exacerbating fatigue and shortness of breath.

Third, the patient demonstrated an improvement in walking capacity, as evidenced by the 6MWT. The 6MWT is a simple and widely used tool for assessing an individual's submaximal functional capacity, which is particularly valuable for patients with advanced diseases and multiple comorbidities who might struggle with complex exercise tests due to low endurance. It measures the distance walked in 6 minutes on a flat surface.[19]

As mentioned, the 6MWT has been shown to correlate with improvements in activities of daily living (ADLs).[20] Regular walking exercises, as part of a structured program, might enhance endurance, muscle strength and overall mobility. In this case, the walking distance improved from 450 meters to 522 meters, indicating a gain in endurance and cardiovascular fitness.

The patient's MET score, which estimates physical activity intensity, increased from 5.2 to 5.6, suggesting a higher capacity for physical activity at a higher intensity. This increase in MET score reflects improved aerobic capacity, overall endurance, and cardiovascular fitness, all of which for enhancing mobility and quality of life. The patient's performance status also improved from 60% to 70%, indicating better self-care ability but still difficulty carrying out normal activities or work tasks.

Despite the observed improvements in airflow, thoracic expansion, walking capacity, and performance status, there was a decline in the FVC, which measures the total volume of air a person can forcefully exhale after taking a deep breath. This was evaluated using the Single Breath Count Test (SBCT), which could serve as a reliable, quick, simple, and easily interpretable alternative to spirometry, has shown a significant correlation with FVC, with reported correlation coefficient of 0.71.[21] The results showed a significant decrease in FVC, decreasing from 2170 mL to 1150 mL.

This decline in FVC may reflect the progressive nature of lung cancer, which leads to damage to the lung parenchyma and a reduction in lung volume. However, it is important to recognize that FVC alone may not fully capture the improvements in respiratory mechanics or functional capacity that can result from rehabilitation efforts.

Other indicators of lung function and physical endurance, such as airflow, thoracic expansion, and walking distance, all demonstrated significant improvement. These findings suggest that the rehabilitation program had a positive

effect on respiratory and functional capacity, even if FVC did not improve.

The decrease in FVC is concerning, as it highlights the progressive nature of lung cancer. However, it remains unclear whether the reduction in FVC is due to disease progression or an isolated effect of the rehabilitation program, as the patient did not undergo further diagnostic testing due to financial constraints. The patient had recently retired, lost his health insurance, thus was unable to access additional medical evaluation. This financial limitation impacts their ability to undergo essential medical evaluations and adjustments to treatment plans.

Overall, this case demonstrates the potential benefit of combining ISE and aerobic exercise to improve functional outcomes in patients with advanced lung cancer. The observed improvements in airflow, thoracic expansion, walking capacity, and performance status indicate that this combined rehabilitation approach can enhance quality of life, even in patients with limited prognosis. However, the observed reduction in FVC warrants further investigation for potential adjustment to the rehabilitation strategy, aiming to clarify the long-term effects of these interventions on lung function in cancer patients and to determine optimal rehabilitation protocols.

## CONCLUSION

The combination of Incentive Spirometry Exercise (ISE) and moderate aerobic exercise proved to be an effective rehabilitation strategy for improving lung function, physical endurance and overall performance.

These findings highlight the potential benefits in the management of lung cancer patients, even during the palliative care phase, by enhancing quality of life, reducing fatigue, and improving physical function. Further studies are needed to better understand the long-term impact of these interventions on lung function and overall survival, as well as to optimize rehabilitation protocols for different stages of the disease.

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Literature Review

# Immunopathogenesis of Pneumocystis Pneumonia (PCP) and Its Clinical Implications

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## Abstract

Pneumocystis pneumonia (PCP) is a serious lung infection caused by Pneumocystis jirovecii, primarily affecting immunocompromised individuals. It remains a major health concern, especially in HIV/AIDS patients and those undergoing immunosuppressive therapy. This review discusses how the immune system responds to P. jirovecii and why immunocompromised individuals are more vulnerable. In healthy individuals, CD4+ T cells, B cells, and macrophages help control the infection. However, in immunocompromised individuals, a weakened immune response allows fungal overgrowth, leading to severe lung damage. The review also covers symptoms, diagnosis, and treatment options. TMP-SMX is the preferred treatment, while alternative drugs are available for those who cannot tolerate it. Understanding the immune response to PCP can help improve treatment and patient care.

**Keywords:** immunocompromised, immunopathogenesis, pneumocystis pneumonia (PCP), T cells

## INTRODUCTION

Pneumocystis pneumonia (PCP) is a fungal infection caused by *Pneumocystis jirovecii* that typically affects individuals with compromised immune systems. The global Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) epidemic that emerged in the 1980s led to a sharp rise in the incidence of PCP, making it a significant contributor to illness and death among immunosuppressed patients.[1] Initially, *P. jirovecii* was classified as a protozoan, but molecular studies later revealed that it is, in fact, a fungal organism.[2]

Despite advancements in antiretroviral therapy (ART) and the widespread use of TMP-SMX prophylaxis, PCP remains prevalent, particularly in non-HIV immunocompromised populations. The ongoing COVID-19 pandemic has further complicated PCP management, as severe SARS-CoV-2 infections induce lymphocytopenia and necessitate corticosteroid use, increasing susceptibility to opportunistic infections like PCP.[3]

The immunopathogenesis of PCP varies between immunocompetent and immunocompromised hosts. In the former, *P. jirovecii* infection is controlled with minimal lung damage, whereas in immunocompromised individuals, unchecked fungal proliferation leads to a severe inflammatory response, causing respiratory distress and lung tissue injury. This review explores the immune mechanisms underlying PCP, its clinical features, diagnostic methods, and current therapeutic strategies.[4]

## PNEUMOCYSTIS PNEUMONIA (PCP)

### Classification and Life Cycle

Previously classified as *Pneumocystis carinii*, the organism causing human infection was renamed *Pneumocystis jirovecii* to differentiate it from rodent-associated species. It exists in two life forms. The cystic form, which is the infectious stage, consists of thick-walled structures measuring 4 to 7 µm in diameter and contains eight ascospores that are released upon rupture. The trophozoite form is smaller, with an irregular shape ranging from 2 to 8 µm, and attaches to alveolar epithelial cells, initiating immune responses.[2–4]

*Pneumocystis* reproduces asexually via binary fission and sexually through meiotic division, forming infectious cysts that spread through airborne transmission. Although primarily affecting the lungs, disseminated infections involving the eyes, ears, thyroid, and bone marrow have been reported in severe cases. The Pneumocystis life cycle is depicted in Figure 1. Description of image detailing cyst and trophozoite forms, their interactions with alveolar epithelium, and modes of transmission.[2,5]

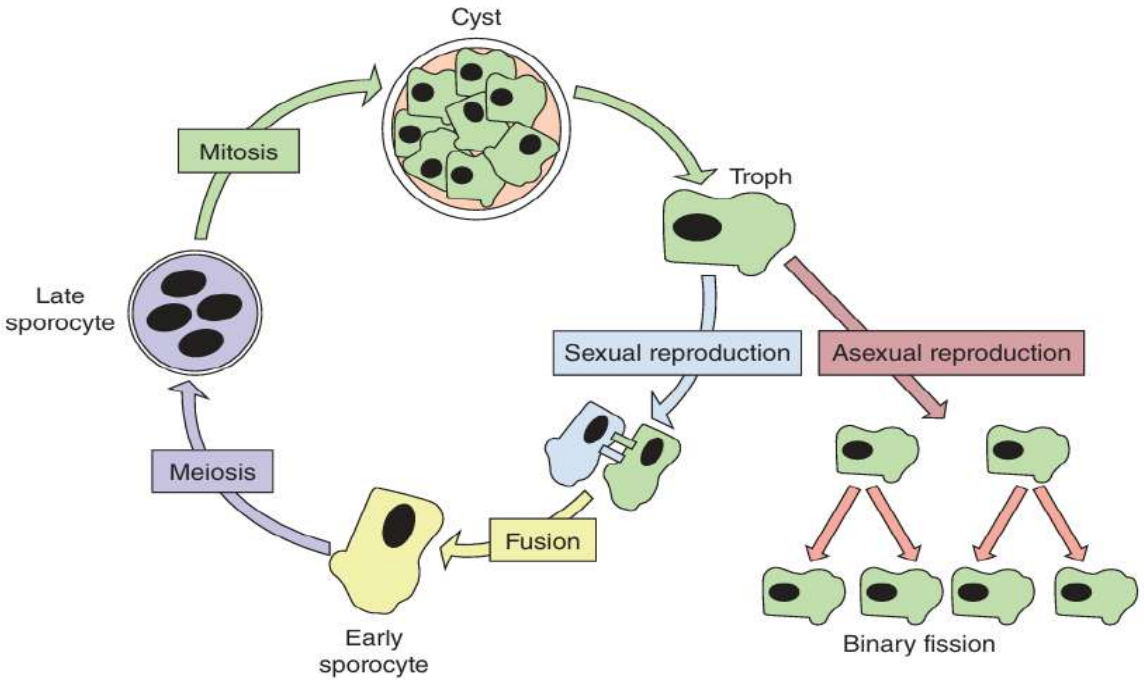


Figure 1. Life cycle of *Pneumocystis* [2]
(Adapted from Eddens et al with modifications by the authors)

## RESPIRATORY IMMUNITY SYSTEM AGAINST INFECTION

The human immune system consists of two primary components: the innate and adaptive immune systems. The innate immune system includes various elements such as the skin epithelium, mucosal surfaces, dendritic cells, macrophages, and natural killer (NK) cells. It serves as the body's first defense against infections and is instrumental in activating the adaptive immune system.[6]

The adaptive immune system, which includes T and B cells, generates cytokines that trigger the activation of neutrophils and dendritic cells to help eliminate pathogens. In the lower respiratory tract, particularly in the alveoli, alveolar macrophages act as antigen-presenting cells (APCs). These cells present antigens to T and B cells in the adaptive immune system, which is crucial in clearing pathogens from the airways.[6]

## IMMUNE RESPONSE TO *PNEUMOCYSTIS* INFECTION IN IMMUNOCOMPETENT INDIVIDUALS

People with a healthy immune system can clear *Pneumocystis* without symptoms. CD4+ T cells help B cells activate M2 macrophages, eliminating the fungus. In contrast, individuals with weakened immunity, such as those with HIV, lose CD4+ T cells, making them more vulnerable to infection. Studies show that mice with CD4+ T cells can clear *Pneumocystis*, while those lacking them develop severe pneumonia. CD4+ T cells and alveolar macrophages are essential for controlling the infection.[7]

### Innate Immunity in Immunocompetent Individuals

When Pneumocystis infects the lungs, antigen-presenting cells (APCs), including macrophages and dendritic cells, identify Pneumocystis components such as the major surface glycoprotein (MSG) and beta-D-glucan (BDG). This recognition activates immune responses through pattern recognition receptors (PRRs), such as Toll-like receptors (TLR2 and TLR4) and C-type lectin receptors (Dectin-1 and Mincle). This interaction stimulates the production of immune signaling molecules, including interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). Afterward, the APCs migrate to lymphoid tissues to initiate the activation of the adaptive immune response.[6,7]

### Adaptive Immunity in Immunocompetent Individuals

CD4+ T cells orchestrate the immune response, promoting M2 macrophage activation and fungal clearance without excessive inflammation. B-cell-mediated antibody responses also contribute to pathogen neutralization and macrophage stimulation.[7,8]

Figure 2 describes how adaptive immunity in immunocompetent individuals protects against *Pneumocystis.* APCs recognize *Pneumocystis* and activate CD4+ T cells, which stimulate B cells in Induced Bronchus Associated Lymphoid Tissue (iBALT) structures. Within iBALT, CD4+ T

cells become follicular T cells (Tfh) to support B cells. Activated macrophages undergo M2 polarization and engulf *Pneumocystis*. CD8+ T cells, polymorphonuclear (PMNs), and eosinophils also aid in clearing the infection. This immune response removes *Pneumocystis* without causing respiratory symptoms.[7,8]

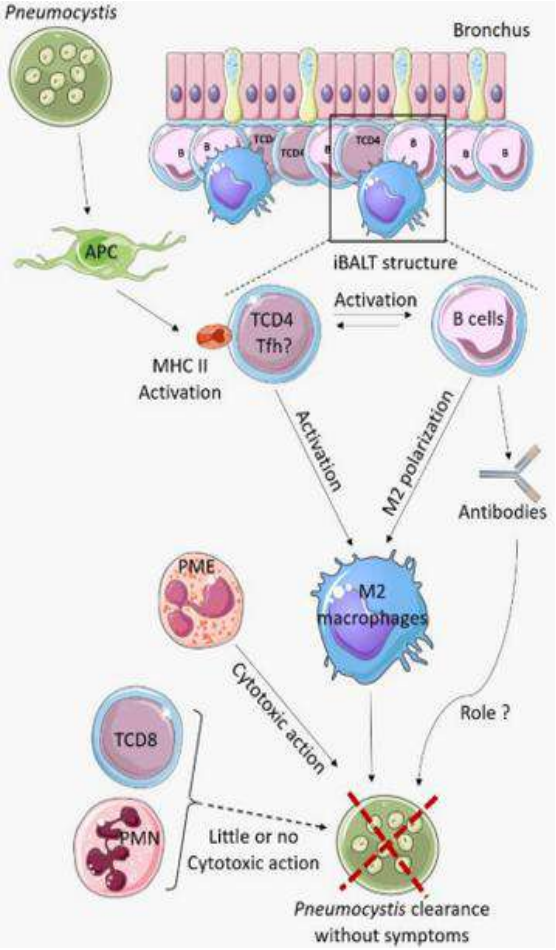


Figure 2. PCP Immunopathogenesis In Immunocompetent Individuals[7]
(Adapted from Charpentier et al with modifications by the authors)

## IMMUNE RESPONSE TO *PNEUMOCYSTIS* INFECTION IN IMMUNOCOMPROMISED INDIVIDUALS

In immunocompromised individuals, the body loses its ability to eliminate *Pneumocystis* effectively, allowing the fungus to multiply in the alveoli. This leads to excessive and ineffective inflammation, causing lung damage and worsening respiratory symptoms.[7]

### Innate Immunity in Immunocompromised Individuals

In HIV patients with PCP, eosinophilia in blood and bronchoalveolar lavage (BAL fluid) correlates with fungal growth two weeks post-infection, though the eosinophils' direct fungicidal role remains unclear.[9] Reduced macrophage numbers and NK cell deficiency impair fungal clearance, while increased TNF-α inhibition (due to immunosuppressive drugs such as glucocorticoids and anti-TNFα) elevates PCP risk. Macrophages and NK cell deficiency leads to increased fungal infections by the fourth week due to reduced IFNγ production.[8–10]

### Adaptive Immunity in Immunocompromised Individuals

CD4+ T cell depletion impairs fungal clearance, shifting the immune response toward a CD8+ T cell and M1 macrophage-dominated reaction. Similarly, B cell deficiency hinders *Pneumocystis* elimination, increasing PCP risk. Monoclonal antibodies targeting B cells further elevate susceptibility. The absence of B cells disrupts antigen presentation and antibody production, particularly IgG, impairing CD4+ T cell activation. Lack of *Pneumocystis*-specific IgG facilitates fungal infections, while reduced IL-10 levels heighten inflammation by increasing Th1 and Th17 activity. This leads to excessive

inflammatory cytokine release, alveolar damage, and respiratory failure.[10,11]

Figure 3 describes how adaptive immunity in immunocompromised individuals against *Pneumocystis*. The lack of CD4+ T cells and B cells weakens the immune response. Th1 cells activate M1 macrophages with IFNγ to clear fungi, while CD8+ T cells and NK cells help by killing *Pneumocystis* directly. M1 macrophages also engulf the fungus, but excessive inflammation can damage lung tissue due to increased PMN infiltration.[7]

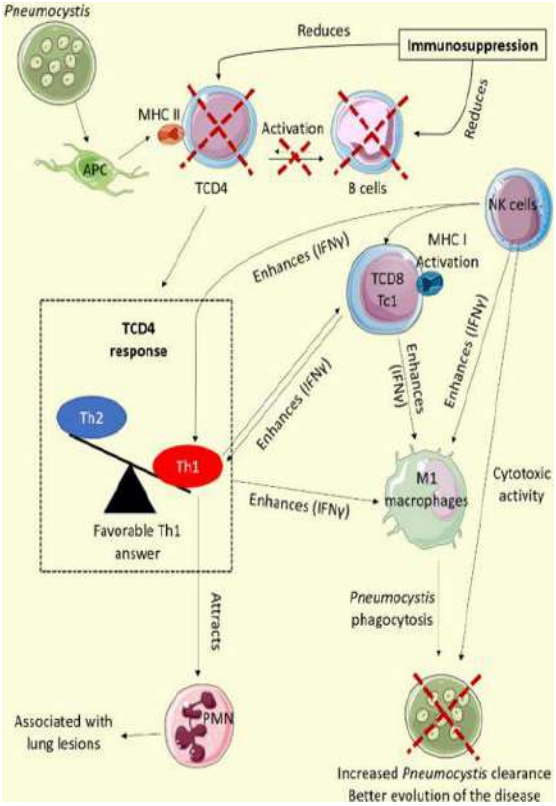


Figure 3. PCP Immunopathogenesis In Immunocompromised Individuals[7]
(Adapted from Charpentier et al with modifications by the authors)

## CLINICAL MANIFESTATIONS

Pneumocystis pneumonia (PCP) presents with nonspecific respiratory symptoms that progressively worsen over days to weeks. The classic triad of PCP includes progressive exertional dyspnea, non-productive cough, and fever. Other symptoms include chest discomfort, fatigue, and weight loss, especially in immunocompromised patients. Patients with HIV-related PCP often exhibit an insidious onset with mild respiratory symptoms, while non-HIV immunocompromised patients experience a more aggressive course, frequently leading to acute respiratory failure requiring mechanical ventilation.[12,13]

In severe cases, PCP can progress to acute respiratory distress syndrome (ARDS), characterized by profound hypoxia, requiring intensive care support. On physical examination, patients may present with tachypnea, tachycardia, and diffuse bilateral crackles on auscultation. Hypoxemia, which worsens with disease progression, is a hallmark feature, often out of proportion to radiographic findings.[12,13]

## DIAGNOSIS

Diagnosing Pneumocystis pneumonia (PCP) is challenging due to its non-specific clinical presentation, necessitating a high index of suspicion in patients with respiratory symptoms and immunosuppressive risk factors. Diagnostic approaches encompass clinical evaluation, radiologic imaging, and laboratory testing. Chest radiographs typically reveal bilateral interstitial infiltrates, which may progress to alveolar consolidation in advanced disease. High-resolution computed

tomography (HRCT) is more sensitive, often showing characteristic ground-glass opacities that can be diffuse or patchy.[13]

Laboratory tests play a crucial role in PCP diagnosis. Serum biomarkers, such as elevated β-D-glucan levels, suggest fungal infection, though specificity is limited. Arterial blood gas analysis often demonstrates hypoxemia with an increased alveolar-arterial gradient. Microbiological testing includes microscopy, where staining methods such as Giemsa and silver stain detect cysts or trophozoites in bronchoalveolar lavage (BAL) or induced sputum samples. Polymerase chain reaction (PCR) assays are highly sensitive for detecting *P. jirovecii* DNA and are particularly useful in cases with a low organism burden.[14,15]

## TREATMENT AND ALTERNATIVE THERAPIES

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the gold standard for treating Pneumocystis pneumonia (PCP). The recommended dosage is 15–20 mg/kg/day of the trimethoprim component, divided into three or four doses, administered either orally or intravenously over a 21-day course.[16,17]

Alternative therapies for TMP-SMX intolerance include pentamidine, atovaquone, and clindamycin plus primaquine. Pentamidine is administered intravenously at 4 mg/kg once daily over 21 days. Atovaquone is administered orally at 750 mg twice daily for 21 days. Clindamycin is administered at 600 mg intravenously or orally every 6 hours, combined with primaquine at 30 mg orally once daily for 21 days.[17,18]

For moderate to severe cases of PCP, characterized by a partial pressure of oxygen ($PaO_2$) below 70 mmHg or an alveolar-arterial (A-a) gradient exceeding 35 mmHg, the use of adjunctive corticosteroids is advised. The standard treatment protocol includes prednisone at 40 mg twice daily for the first five days, followed by 40 mg once daily for the next five days, and then 20 mg once daily for 11 days, completing a 21-day treatment course. This method helps reduce inflammation and has been shown to enhance survival outcomes.[18]

Immunotherapy has shown promise as an adjunctive treatment for PCP, especially in individuals with compromised immune systems. One emerging strategy involves the use of monoclonal antibodies targeting immune checkpoint inhibitors, such as pembrolizumab and nivolumab. These medications, primarily used in cancer treatment, work by blocking the programmed cell death-1/programmed cell death ligan-1 (PD-1/PD-L1) pathway, which typically dampens T-cell activity.[19,20]

By inhibiting this pathway, the immune system may be better equipped to fight infections like PCP in cancer patients, particularly in patients with significantly low T-cell counts. While clinical studies on the application of immune checkpoint inhibitors for PCP are still limited, preliminary results indicate that these drugs might enhance immune responses and reduce the occurrence of recurrent infections in high-

risk populations, including those with HIV or transplant recipients.[19,20]

Another potential immunotherapeutic approach is the use of intravenous immunoglobulin (IVIG), which contains antibodies against various pathogens, including *Pneumocystis jirovecii*. IVIG has been studied as a potential therapy for individuals with recurrent or treatment-resistant PCP, particularly in cases of B-cell deficiencies or impaired antibody production. IVIG provides passive immunity by supplying exogenous antibodies, which can aid in neutralizing and eliminating the pathogen.[21]

Some clinical studies have suggested that IVIG therapy can improve clinical outcomes and decrease mortality in immunocompromised patients with PCP by boosting the immune response. However, more research, including randomized controlled trials, is needed to determine its optimal use and effectiveness in managing PCP.[21]

## CONCLUSION

Pneumocystis pneumonia is a life-threatening infection, especially for people with weak immune systems. CD4+ T cells play a crucial role in fighting *P. jirovecii*, and their absence leads to severe disease. Early diagnosis using imaging and lab tests is essential for proper treatment. TMP-SMX is the most effective drug, but other options like pentamidine and atovaquone are available. Severe cases may require corticosteroids to reduce lung inflammation.

Understanding the immunopathogenesis of PCP is crucial for developing targeted therapies, immunotherapies, and improved diagnostic strategies. Future research should focus on novel antifungal agents with fewer side effects, host-directed therapies to modulate inflammatory responses, and improved prophylactic strategies for high-risk populations.

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