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Original Article

# Profile of COVID-19 Patients at Arifin Achmad Hospital, Riau Province Between January 2021 and June 2021

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## Abstract

**Background:** Coronavirus disease 2019 (COVID-19) is a disease caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously called 2019 novel coronavirus) which was first identified in Wuhan City, Hubei Province, China. World Health Organization declared COVID-19 a global pandemic on March 12 2020 and until June 2021 there were 184 million cases with 3.9 million deaths worldwide. In Indonesia, until June 2021 there have been 2.2 million positive cases of COVID-19 and 60 thousand deaths.

**Method:** The data collection method used in this study is a descriptive cross-sectional approach. According to the inclusion criteria, samples were collected for six months, and the results are shown as a distribution table.

**Results:** The number of patients treated for the period from January to June 2021 totaled 1,442 people. The highest number of patients treated according to age was middle-aged (40.6%) and children (1.1%). The number of COVID-19 patients based on length of treatment from January to June was suspected (2-4 days) 28.13%, confirmed (5–45 days) 61.6%, discharged at own request 9.78%, referred 0.48%. The number of cured COVID-19 patients being treated at the Arifin Achmad Hospital in Riau Province from January to June 2021 has recovered 75.9% and died 13.7%.

**Conclusion:** In Indonesia, until June 2021 there have been 2.2 million positive cases of COVID-19 and 60 thousand deaths. Riau Province as of June 2021 has recorded 70,520 confirmed cases and 1,931 deaths. The Arifin Achmad Pekanbaru General Hospital from March 2020 to June 2021 recorded 1,524 confirmedcases and 148 deaths.

**Keywords:** confirmed cases, COVID-19, profile of COVID-19 patients

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously called 2019 novel coronavirus) which was first identified in Wuhan City, Hubei Province, China.[1]

This virus is a single-stranded ribonucleic acid (single-chain RNA) virus that can be isolated from several types of animals, the last being that this virus originated in bats and then moved to humans. This disease was first reported to the World Health Organization (WHO) on 31 December 2019.[1]

World Health Organization declared COVID-19 a global pandemic on March 12, 2020, and until June 2021 there were 184 million cases with 3.9 million deaths worldwide.[2,3] In Indonesia, until June 2021 there have been 2.2 million positive cases of COVID-19 and 60 thousand deaths.[4] Riau Province as of June 2021 has recorded 70,520 confirmed cases and 1,931 deaths.[5] The Arifin Achmad Pekanbaru General Hospital from March 2020 to June 2021 recorded 1,524 confirmed cases and 148 deaths.[6]

Based on the severity of the case, COVID-19 is divided into asymptomatic, mild, moderate, severe and critical. Asymptomatic COVID-19 patients are in the mildest condition and no clinical symptoms are found in patients. Mild symptoms such as fever, cough, sore throat and no pneumonia.

Moderate symptoms such as fever >38°C, persistent cough, shortness of breath with pneumonia symptoms and $SO_2$ >93% in room air. Severe symptoms such as fever >38°C, persistent cough, respiratory rate >30x/minute (respiratory distress) with severe pneumonia and $SO_2$ <93% in room air. COVID-19 patients with critical conditions have symptoms of acute respiratory distress syndrome (ARDS), sepsis and septic shock.[7]

There is very strong evidence that changes in the immune response are correlated with clinical manifestations in COVID-19 infection. The clinical manifestations of COVID-19 patients have a wide spectrum, ranging from asymptomatic, mild symptoms, pneumonia, ARDS, and sepsis to septic shock. Approximately 80% of cases were classified as asymptomatic as well as mild symptoms, 13.8% experienced moderate and severe symptoms, and 6.2% of patients were in critical condition.[8]

Mild symptoms were defined as patients with uncomplicated acute upper respiratory tract infection with symptoms of fever, fatigue, cough, malaise, sore throat and anosmia and did not require oxygen supplementation. In some cases, patients also complain of diarrhea and vomiting.[9,10]

Fever is caused by SARS-CoV2 which is recognized by macrophage cells so that the activation of macrophages activation syndrome (MAS) induces cytokines and chemokines that can invade the hypothalamus thereby increasing the set point of body temperature to increase according to the levels of pyrogen exposed.[9]

Likewise, fatigue and malaise are triggered by the innate immune response to the SARS-CoV-2 antigen. Colonization of the SARS-CoV-2 virus causes edema and inflammation of the oropharyngeal mucosa causing symptoms of sore throat and painful swallowing. Colonization

creates inflammation of the nasopharyngeal mucosa which affects the olfactory nerve (NI) and causes disturbance of smell or anosmia. Colonization that causes inflammation of the mucosa and papillae of the tongue then affects the facial nerve (N.7) causing disturbances of taste or augesia.[9]

Expression of the angiotensin-converting enzyme (ACE2) receptor on epithelial cells in various organs causes a wide spectrum of clinical manifestations of COVID-19. It was reported that the expression level of ACE2 receptors in gastrointestinal and kidney epithelial cells was higher than expression in epithelial cells of other organs, so symptoms of heartburn, nausea, vomiting and diarrhea were also found in COVID-19 patients.[11]

Symptoms of shortness of breath or no chest discomfort are caused by acute inflammation due to the innate immune response in the alveoli which interferes with the respiratory ventilation system resulting in ventilation and perfusion mismatch (V/Q mismatch) and shunting which causes hypoxemia.[12]

Moderate symptoms are defined as patients with clinical signs of pneumonia without signs of hypoxemia ($SpO_2$ >92%) but need oxygen supplementation. In this degree of COVID-19, there are manifestations of silent hypoxia or happy hypoxia. The patient did not complain of tightness or chest discomfort but showed decreased saturation. This is caused by the damage that occurs in the alveoli with an even distribution so that symptoms of shortness of breath do not arise.[13–16]

Severe symptoms are defined as patients with clinical signs of pneumonia, plus one of the following symptoms, namely increased respiratory rate >30x/minute, severe respiratory distress, or oxygen saturation <93% without oxygen support. Critical symptoms are defined as patients with clinical pneumonia and complications such as ARDS, multi-organ dysfunction syndrome (MODS), sepsis or septic shock.[9,12–17]

A critical degree of COVID-19 occurs after the 7th day of the incubation period. This situation is caused by many factors such as SARS-CoV-2 virulence, strains, mutations, viral load, and viral titers with innate and adaptive immune response factors in patients.[9,12–17]

The course of the disease begins with an incubation period of about 5 days. Then the higher the virus titer causing fever and other symptoms according to severity. Then if there is an increase in the immune response followed by a collection of symptoms of chest discomfort with decreased saturation, this condition enters the pneumonia phase. During this phase, there is also an increase in inflammatory markers and hypercoagulation begins.[18] If not resolved, the next phase is systemic inflammation, a cytokine storm occurs which results in ARDS, sepsis, and other complications.[19]

## METHOD

The study is a cross-sectional descriptive study using secondary data

collected from patients in the PINERE (*penyakit infeksi new emerging dan re-emerging*) Ward of the Arifin Achmad Hospital in Pekanbaru between January 2021 and June 2021. Patients who satisfied the inclusion criteria, were all patients treated in the PINERE 1, PINERE 2, PINERE 3 wards and the RICU from January to June 2021.

## RESULTS

The number of patients treated for the period from January to June 2021 totaled 1442 people. The highest number of patients treated according to age was middle age as much as 40.6% and childhood as much as 1.1%.

Table 1. Age Characteristics of Research Samples (N=1442)

| Age (years) | N | % |
|---|---|---|
| Toddler (0-5) | 121 | 8.4 |
| Childhood (6-11) | 16 | 1.1 |
| Adolescence (12-25) | 92 | 6.4 |
| Young age (26-45) | 456 | 31.6 |
| Middle age (46-65) | 585 | 40.6 |
| Old age (>65) | 172 | 11.9 |

Table 2. Characteristics of PINERE Ward Patients Based on Length of Treatment Days (N=1442)

| Characteristics of length of stay (days-months) | N | % |
|---|---|---|
| Suspect (2-4 days) | 399 | 27.7 |
| Confirmed (5-45 days) | 892 | 61.9 |
| Discharged at Own Request | 144 | 9.99 |
| Referred | 7 | 0.48 |

Table 3. Recovery and Died Patients (N=1442)

| Characteristics of patients | N | % |
|---|---|---|
| Recovery/ Discharged | 1.094 | 75.9 |
| The patient died | 197 | 13.7 |

## DISCUSSION

Between January 2021 and June 2021, 1442 patients were hospitalized and received treatment at Arifin Achmad Hospital Pekanbaru's PINERE ward. This study is based on age 585 (40,6%) patients in middle age and 456 (31,6%) patients in young age. According to data from the Ministry of Health Indonesia, the highest positive cases of COVID-19 were experienced by the age group 31-45 years, namely 29,05% of cases. Meanwhile, positive cases for the age group 0-5 were 2,9% cases.[4]

In this study group, there were 8,4% inward patients that hadn't been confirmed the COVID-19 status until discharged. There were 61.6% of cases confirmed COVID-19 with a mean length of stay was 5 to 45 days.

The number of cured COVID-19 patients being treated at the Arifin Achmad Hospital in Riau Province from January to June 2021 has recovered 75.9%. As of 24 November 2021, the total number of confirmed cases of COVID-19 in the world is 258,164,425 cases with 5,166,192 deaths (CFR 2.0%) in 204 affected countries and 151 community transmission countries and there have been 194,102,700 patients (75.2%) have recovered from the disease.[2,3]

The recovery rate of patients in the subjects of this study was almost the same as global conditions. This is different from the recovery rate in Indonesia based on data from the Ministry of Health of the Republic of Indonesia which reached

96.4%. The Ministry of Health of the Republic of Indonesia has taken action to improve efforts to deal with COVID-19 in Indonesia, referring to WHO temporary guidelines on the novel coronavirus.[4]

The number of COVID-19 patients treated at Arifin Achmad Hospital in Riau Province from January to June 2021 who died was 13,7%. In Indonesia, until June 2021 there have been 2.2 million positive cases of COVID-19 and 60 thousand deaths.[4] Riau Province as of June 2021 has recorded 70,520 confirmed cases and 1,931 deaths.[5]

The Arifin Achmad Pekanbaru General Hospital from March 2020 to June 2021 recorded 1,514 confirmed cases and 148 deaths.[6] This means that 2.16% of confirmed COVID-19 cases were treated at Arifin Achmad General Hospital and 7.7% of deaths due to COVID-19 in Riau province were recorded. Further research is needed to determine the cause of death in the other 6% of patients.

## CONCLUSION

Based on the results and discussion that has been described in this study, the results obtained from 1442 samples with various characteristics, it was concluded that the highest age group was obtained at the age of 26-45 years and 46-65 years. The number of confirmed COVID-19 patients based on the length of treatment from January to June about 5-45 days was 61.6%. The number of cured COVID-19 patients being treated at the Arifin Achmad Hospital in Riau Province from January to June 2021 has recovered 75,9%. Medical services are advised to provide appropriate action and adequate therapy, to avoid the severity and complications that will arise.

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Original Article

# Carcinoembryonic Antigen (CEA) and Cancer Antigen 125 (CA-125) as Diagnostic Biomarkers for Malignant Pleural Effusion

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## Abstract

**Background:** The etiology of pleural effusion is very important in malignant pleural effusion management and prognosis. Pleural fluid cytology examination is a simple diagnostic tool and has been widely used to differentiate the etiology of pleural fluid with high specificity albeit its relatively low sensitivity. The use of tumor markers for malignant pleural effusion in Indonesia is still sparse. This study was intended to determine the sensitivity and specificity of CEA and CA-125 examinations in diagnosing malignant pleural effusion.

**Method:** This was an observational analytic study with a cross-sectional approach to find the diagnostic value of CA-125 and CEA of pleural fluid in malignant pleural effusion. Subjects were patients with suspicion of malignant pleural effusion who underwent treatment in the emergency room, polyclinic, and inpatient ward at RSDM from October - November 2022.

**Results:** CEA value with a cutoff of ≥32.00 had a sensitivity of 83.3%; specificity of 87.8%; PPV of 90.9%; NPV of 77.8% with an accuracy of 85.0% (P=0.001), a CA-125 value with a cutoff of >152.40 had a sensitivity of 83.3%; specificity 81.3%; PPV 87.0%; NPV 76.5%; with an accuracy of 82.5% (P=0.001). An increase in CEA and CA-125 signified a significant risk of malignant pleural effusion (P<0.05). Patients with increased CEA and CA-125 had 105 times the risk of developing malignant pleural effusion.

**Conclusion:** CEA ≥32.00 and CA-125 >152.40 are potential biomarkers to predict malignant pleural effusion with CEA having better specificity than CA-125.

**Keywords:** CA-125, CEA, lung cancer, malignant pleural effusion

## INTRODUCTION

Pleural effusion often presents as a diagnostic challenge for medical doctors. Differentiating exudates from transudates has always been the main concern in the diagnostic process which requires physical chemistry evaluation from the fluid sample and the biochemical parameters such as total protein, lactate dehydrogenase (LDH), bilirubin, and cholesterol. Determining the exudative or transudative nature of the pleural fluid paves a long way in diagnosing the causative disease.[2]

Pleural effusion may appear benign or malignant and each form has its different management system and prognostic value. Pleural fluid cytology has a high sensitivity for detecting the presence of malignant cells in lung cancer (79.0%), but the result is prone to false negatives when pleural thickening is present and the invasive procedure of sample collection can be uncomfortable for the patients.[3]

Tumor markers hold a promising future as an alternative to pleural fluid cytology for differentiating pleural effusion etiology. These prospective markers include carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), cancer antigen 15-3 (CA 15-3), cancer antigen 19-9 (CA 19-9), cancer antigen 72-4 (CA 72-4), cytokeratin 19 fragments 21-1 (CYFRA 21-1), neuron-specific enolase (NSE), and squamous cell carcinoma antigen (SCCA). However, the clinical value of tumor markers in pleural effusion fluids has not been widely discovered.[4]

Pleural effusions which are benign in nature are twice as common as their malignant counterpart which has multiple manifestations and origins, presenting themselves as a diagnostic challenge. A negative cytologic examination often requires more procedures to confirm the etiology of a pleural effusion.

Multiple studies by Yataco in 2005,[5] Rasyid in 2012,[6] and Halim in 2009[7] reported the use of tumor markers as alternative diagnostic methods. Tumor markers had previously been mostly used for cancer patient screening, prognostic evaluation, and treatment monitoring. Due to the sheer amount of research on the use of tumor markers in malignant pleural effusion patients, more study is needed.

This study aimed to explore the sensitivity and specificity of CEA and CA-125 in diagnosing malignant pleural effusion. Hoped to establish CEA and CA-125 as additional and rapid diagnostic tools for patients with suspected pleural effusion and no malignant cell found in pleural fluid cytology or histopathological examinations, therefore minimizing the need for invasive procedures.[7]

## METHOD

This study is an analytical observational study with a cross-sectional approach conducted by dr. Moewardi Regional Hospital, Surakarta from October-November 2022 to test the diagnostic performance of CEA and CA-125 in predicting malignant pleural fluid. The examination referred to as the gold standard is pleural fluid cytology, i.e. positive histopathological finding of malignant cells in pleural fluid. This study has been approved by dr. Moewardi Regional Biomedical Research Ethics Committee as stated in ethical clearance letter number 1.239/IX/HREC/2022.

Subjects in this study were patients who were undergoing treatment in the hospital's emergency room, clinic, and ward. Pleural exudative fluid was taken from patients with suspected malignant pleural effusion at the dr. Moewardi Regional Hospital Clinical Pathology Laboratory and a pleural fluid cytology

examination were done at the dr. Moewardi Regional Hospital Pathologic Anatomy Laboratory in October 2022.

The sample size was counted using the sample size formula for the diagnostic study with a 95% confidence interval (CI). The minimum sample size was intended for patients with positive diagnoses according to the gold standard. Based on the calculation, required a minimum of 26 subjects. Study subjects were enrolled using consecutive sampling methods, in which eligible subjects were recruited until the bare minimum was met.

Eligible subjects in this study were adult patients above 18 years old, who had exudative pleural effusion, suspected of malignant pleural effusion from one or more of the following criteria: thorax x-ray or computed tomography (CT) scan which showed pleural effusion with a description of lung tumor or metastasis, thorax x-ray or CT scan which showed massive pleural effusion with or without lung tumor or metastasis, and thoracentesis which produced yellow or serosanguinous fluid.

Excluded patients with pneumonia and lung tuberculosis, pleural effusion patients with transudative fluid, comorbidities such as renal failure, heart failure, cirrhosis, and pancreatitis, patients with other malignancies outside of the lung, and pleural fluid analysis determined as invalid due to volume being too small or decontamination.

Used 2x10 cc of the pleural fluid sample through thoracentesis for CEA and CA-125 examination. The pleural fluid was then sent to the clinical pathology laboratory to be stored in an aliquot at -20°C.

The samples were then centrifuged at 2000 rotations per minute (rpm) for 10 minutes. CEA examination was done using Cobas ® E411 from F. Hoffmann-La Roche AG through the electrochemiluminescence immunoassay (ECLIA) principle.

CA-125 examination was done through enzyme-linked immunosorbent assay (ELISA) using mini VIDAS from bioMérieux SA which used a strip reagents system with enzyme-linked fluorescent assay (ELFA) principle for 1 hour. Hemoglobin, leukocyte, platelet, and lymphocyte extraction was done using Mindray BC 1800 for 10 seconds.

Descriptive analysis to see the characteristics of the samples based on their malignancy status. Continuous variables such as CA-125, CEA, and pleural fluid cytology values were analyzed through the Kolmogorov-Smirnov normality test based on their average and deviation standard value. Normally distributed data would be analyzed through an independent t-test, while unevenly distributed data would be analyzed through the Mann-Whitney test.

Also conducted area under curve (AUC) analysis for CEA and CA-125 to determine the cut-off use with the best sensitivity, specificity, and performance value. Diagnostic tests for CEA and CA-125 would be done using a 2x2 table to determine their sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

## RESULTS

Obtained 40 eligible patients during the study mostly consisting of males (58.3%) in the malignant group. The number of male and female patients in the non-malignant group were even (50.0%). Chi-square analysis revealed no significant differences among the study groups based on gender. Most subjects in the malignant group had mass in their radiologic examination (66.7%) while in the non-malignant group, only 6 patients had mass (37.5%).

Table 1. Subjects Characteristics

| Variables | Malignant (n=24) | Benign (n=16) | P[a] |
|---|---|---|---|
| Gender | | | |
| Male | 14 (58.3%) | 8 (50.0%) | 0.604 |
| Female | 10 (41.7%) | 8 (50.0%) | |
| Radiologic findings | | | |
| Mass | 16 (66.7%) | 6 (37.5%) | 0.069 |
| No mass | 8 (33.3%) | 10 (62.5%) | |

Note: [a]Chi-square result

The average age was 54.67±13.58 years old for the malignant group with a median of 55.00 years old and 54.00±13.87 years old for the non-malignant group with a median value of 57.50 years old.

Mean and median CEA value was found to be higher in the malignant group than in the non-malignant group [198.08±119.66 vs 24.04±39.74 and 267.65 (1.80-318.60) vs 14.00 (0.10-157.20), respectively]. The difference in the CEA value was found to be statistically significant (P<0.001).

The mean and median CA-125 value in the malignant group [340.86±150.85 and 416.15 (37.43-508.40)] was also found to be higher than the non-malignant group [116.00±62.64 and 122.70 (26.10-219.90)]. Found that the difference in CA-125 value was statistically significant (P<0.001).

Conducted ROC analysis to figure out the optimum cut-off point for CEA and CA-125. An AUC value of 0.845 with a cut-off value ≥32.00 was found for CEA with 83.3% sensitivity, 87.8% specificity, 90.9% PPV, 77.8% NPV, and 85.0% accuracy (P≤0.001).

Table 2. Subjects Characteristics

| Variables | Malignant (n=24) | Benign (n=16) | P |
|---|---|---|---|
| Age | | | |
| Mean±SD | 54.67 ±13.58 | 54.00 ±13.87 | 0.881[b] |
| Median (min-max) | 55.00 (25.00-76.00) | 57.50 (24.00-70.00) | |
| CEA | | | |
| Mean±SD | 198.08 ±119.66 | 24.04 ±39.74 | <0.001*[c] |
| Median (min-max) | 267.65 (1.80-318.60) | 14.00 (0.10-157.20) | |
| CA-125 | | | |
| Mean±SD | 340.86±150.85 | 116.00±62.64 | <0.001*[c] |
| Median (min-max) | 416.15 (37.43-508.40) | 122.70 (26.10-219.90) | |

Note: SD= standard deviation; min= minimum value; max= maximum value; *P<0.05; [b]normally distributed data, comparative analysis through independent t-test; [c]uneven distributed data, comparative analysis through Mann-Whitney test

Table 3. Odds Ratio Analysis for CEA and CA-125

| | Malignancy | | OR (95% CI) | PPV (%) | NPV (%) | P |
|---|---|---|---|---|---|---|
| | Malignant (n=24) | Benign (n=16) | | | | |
| CEA | | | | | | |
| ≥32.00 | 20 (83.3%) | 2 (12.5%) | 35.00 (5.62-218.11) | 90.0 | 77.8 | <0.001* |
| <32.00 | 4 (16.7%) | 14 (87.5%) | | | | |
| CA-125 | | | | | | |
| ≥152.40 | 20 (83.3%) | 3 (18.8%) | 21.67 (4.15- 113.02) | 87.0 | 76.5 | <0.001* |
| <152.40 | 4 (16.7%) | 13 (81.3%) | | | | |

Note: CEA=carcinoembryonic antigen; CA-125=cancer antigen-125; OR=odds ratio

This result showed that CEA ≥32.00 manifested a malignant pleural effusion. ROC analysis for CA-125 revealed an AUC of 0.870 using a cut-off value >152.40 with 83.3% sensitivity, 81.3% specificity, 87.0% PPV, 76.5% NPV, and 82.5% accuracy (P≤0.001). This demonstrated that CA-125 >152.40 marked a possible malignant pleural effusion.

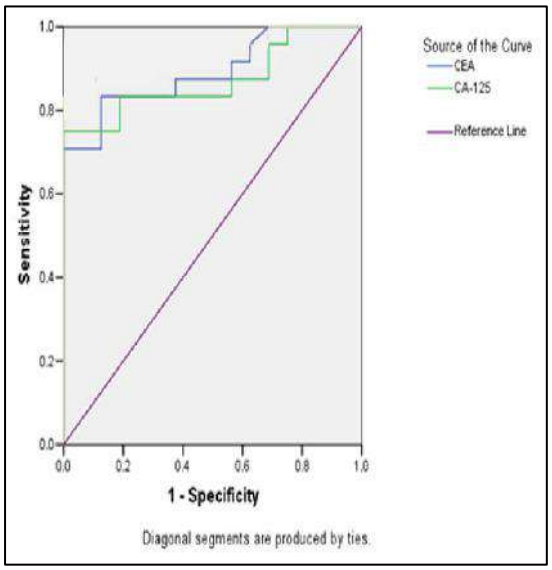


Figure 1. ROC Analysis for CEA and CA-125

Founded that patients with CEA ≥32.00 were 35 times more likely to develop malignant pleural effusion (OR=35.00; 95% CI=5.62-218.11; P≤0.001) and patients with CA-125 ≥152.40 were 21.67 times more likely to have malignant pleural effusion (OR=21.67; 95% CI=4.15-113.02; P≤0.001).

## DISCUSSION

Carcinoembryonic antigen is an underutilized biomarker to detect lung cancer prognosis and its use is still debatable.[8] The value of CEA often recedes after birth and it is not uncommon for healthy adults to have little to no CEA. Blood, pleural fluid, cerebrospinal fluid, and peritoneal fluid may serve as samples for CEA examination. A high CEA value may indicate a certain type of cancer including lung cancer.[9] A previous study by Sun et al in 2020 stated that CEA is significantly raised in lung cancer compared to healthy subjects and subjects with benign lung tumors.[10]

Most patients in this study were male (58.3%) compared to female (41.7%). Data from GLOBOCAN 2020 stated that 1,435,943 males had lung cancer compared to 770,828 females.[11] Another hospital-based study from 100 hospitals in Jakarta also showed that lung cancer is the most common disease in men, the 4$^{th}$ most common disease in females, and the main cause of mortality in males and females.[12]

The risk of developing lung cancer increases along with age. Lung cancer may appear at a younger age, but it is unlikely to develop in people aged below 40 years old. The risk of lung cancer increases per year after 40 years old.[13] In this study, it is found that the average age of patients suffering lung malignancy is 54.67±13.58 conforming to the age at risk for lung cancer being above 40 years old. Elderly people tend to have shorter telomeres which contributes to DNA damage and hence, cancer development.[14]

Invading cancer cells often cause CEA estuary in the pleural space, therefore making it a good biomarker for malignant pleural effusion. Our study revealed that malignant pleural effusion patients had a significantly higher CEA than benign pleural effusion patients (P≤0.001). This finding is similar to a study by Cheng and colleagues in 2021 which stated that CEA performed well as a diagnostic marker for malignant pleural effusion with a sensitivity and specificity ratio of 80%:92%.[15]

CA-125 also known as mucin-16 (MUC16) is a protein that is coded by the MUC16 gene in humans. CA-125 is mostly found on the surface of the ovary, inflammatory cells, and non-inflammatory cells. The proliferation of these cells causes CA-125 to be released. CA-125 itself has been commonly used as a specific marker for ovary tumors.[16]

Our study obtained a significant difference in CA-125 value between the malignant and benign groups where the malignant pleural effusion patients had a higher value than the benign ones (P≤0.001). The same result was presented in a study by Shalaby and colleagues in 2015 which showed that pleural fluid CA-125 had a sensitivity of 99% and 78% specificity. This study found CA-125 in malignancy and lung tuberculosis patients and therefore could be utilized in diagnosing malignant cases.[16]

Another study by Zhang and colleagues in 2020 found that biomarkers from pleural fluid samples were superior to pleural fluid cytology in figuring malignant pleural fluid, with CEA being the most effective indicator for lung cancer associated with malignant pleural effusion at the cut-off point of 5.23 ng/ml.[17]

Another previous study by Sthaneshwar and colleagues in 2002 found another cut-off point for CEA and CA-125 in differentiating malignant pleural effusion from benign pleural effusion. These cut-off points were 5.1 ng/ml and 1707 IU/ml, respectively. The study obtained a 64% sensitivity and 98% specificity for CEA, while CA-125 had 36% sensitivity and 94% specificity.[17]

The subjects of this study have different types of lung malignancy and were diagnosed at different stages at the time of study. Hence, there is an overlooked potential that certain patients may have different possibilities of malignant cells being present in pleural fluid as well as having increased CEA and/or CA-125. Also unable to investigate any possible underlying causes of the pleural effusion besides malignancy. This study did not include patients with transudative pleural effusion, therefore the

results from this study may not apply to transudative pleural effusion patients. Subjects in the benign pleural effusion were also not differentiated based on the etiology of the pleural effusion due to the low number.

## CONCLUSION

A high CEA (≥32 µg/L) and/or CA-125 (>152.40) may present as a diagnostic predictor for malignant pleural effusion. CEA had a better sensitivity, specificity NPV, and PPV than CA-125.

## ACKNOWLEDGMENTS

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Case Report

# The Role of Emergency Pleural Drainage in the Obstructive Shock in a Left Massive Hemothorax: A Case Report

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## Abstract

**Background:** Spontaneous hemothorax is much less common, and the causes include malignancies, anti-coagulant medications, vascular ruptures, endometriosis, pulmonary infarctions, adhesions with pneumothorax, and hematologic abnormalities such as hemophilia. This report presented a confirmed case of obstructive shock in a patient with massive left hemothorax and elaborated on the role of emergency pleural drainage in this particular clinical situation.

**Case:** Reported a case of a 56-year-old man with a 2-month history of dyspnea, leg swelling, abdominal bloating, hemoptysis, and fatigue. Physical examination revealed an asymmetrical chest wall expansion with a predominance of abdominal breathing. His neck and face were markedly discolored and swollen, with distended veins. The left hemithorax was dull on percussion and, on auscultation, significantly reduced air entry at the left lung base.

**Discussion:** The patient was given an $O_2$ non-rebreathing mask (NRBM) on arrival. The patient was administered two vasopressors (dopamine, 2.5 mcg/kg per body weight/minute, and norepinephrine, 0.1 mcg/kg per body weight/minute). Given the patient's hemodynamic instability and high probability of imminent death. The patient required urgent intervention to relieve the obstructive shock. The surgical department was inserted to treat the massive hemothorax, which drained approximately 1.5 liters of blood. The patient received supplementary oxygen, antibiotics, and furosemide.

**Conclusion:** The pleural fluid drainage alleviated the dyspnea. As supportive therapy, the patient received oxygen, antibiotics, and furosemide. On the follow-up, the mediastinal shift had resolved simultaneously.

**Keywords:** emergency pleural drainage, hemothorax, obstructive shock

## INTRODUCTION

Severe blunt force to the chest frequently leads to extensive thoracic bleeding, or hemothorax, primarily resulting from numerous rib fractures. Additionally, it can cause injuries to the pulmonary, cardiovascular, and diaphragmatic systems.[1]

Hemothorax is characterized by pleural fluid containing a hematocrit equal to or exceeding 50% of the hematocrit in the peripheral blood.[2] A pleural effusion is characterized by fluid accumulation between the visceral and parietal layers of the pleura.[3] A pleural effusion is classified as hemorrhagic when the red blood cell count in the pleural fluid exceeds 100,000 cells/μl.[2]

Spontaneous hemothorax is much less common, and the causes include malignancies, anti-coagulant medications, vascular ruptures, endometriosis, pulmonary infarctions, adhesions with pneumothorax, and hematologic abnormalities such as hemophilia.[4]

The prevailing cause of trauma typically involves either blunt or penetrating injuries to structures within or outside the thoracic region, leading to hemorrhagic entry into the thoracic cavity. Hemorrhage can arise from various sources, including the chest wall, intercostal or internal mammary arteries, great vessels, mediastinum, myocardium, lung tissue, diaphragm, or abdominal region.[5]

A substantial hemothorax has the potential to elevate hydrostatic pressure, applying force to the vena cava and pulmonary parenchyma. Elevated hydrostatic pressure can disrupt preload, elevate pulmonary vascular resistance, and ultimately lead to tension hemothorax.[5] These processes contribute to hemodynamic instability, cardiovascular collapse, and fatality.

There are few reports of spontaneous hemothorax causing obstructive shock.[4] Obstructive shock is linked to the mechanical obstruction of blood flow to the heart, particularly affecting the left ventricle. The typical pathophysiology of obstructive shock involves a decrease in the preload of the left ventricle (LV).[6]

Elevated intrathoracic pressure interferes with venous return in tension pneumothorax, while heightened right ventricular (RV) afterload obstructs blood flow from the right to the left heart in pulmonary embolism. Diminished cardiac compliance disrupts the heart's diastolic filling in cardiac tamponade.[6]

The decrease in LV preload results in a relative elevation of both LV contractility and heart rate, but ultimately, stroke volume and cardiac output (CO) decrease.[6] Due to the blockage of blood flow, swollen jugular veins and an enlarged inferior vena cava (IVC) are frequently noticeable during physical examinations or bedside sonography.[4]

Obstructive shock is characterized by the critical need to identify the obstructive cause for effective management, and the response to treatment is rapid. Moreover, patients with impaired consciousness or severe shock require airway management.

The initial stage of circulatory support involves volume resuscitation. In patients experiencing obstructive shock, the venous system is similar to patients with volume overload.[7]

The jugular vein and inferior vena cava are swollen, and the pressure of both central venous and pulmonary artery occlusions increases.[4] Nevertheless, their cardiac output can respond to volume resuscitation due to the heightened cardiac filling pressure in obstructive shock. Rapid recognition and treatment of the obstructive shock are crucial for the outcome, and if blood pressure does not improve promptly, vasopressors can be empirically administered.[6]

This report aimed to present a case of obstructive shock in a patient with a significant accumulation of blood in the left pleural cavity (massive left hemothorax) who underwent urgent pleural drainage. It detailed the role of promptly performing emergency pleural drainage in addressing this type of shock, and the substantial accumulation of blood on the left side will be described.

## CASE

The data were collected using the patient's medical records and a direct examination. Reported a case of a 56-year-old male who arrived at a local hospital after experiencing symptoms such as shortness of breath, swollen legs, a bloated abdomen, coughing up blood, and overall fatigue for two months. The patient denied any weight loss, chest pain, or night sweats. The patient had no history of previous disease or trauma.

Upon the patient's admission, the results of the routine blood tests were as follows: Hemoglobin level was 11.9 g/dL (within the normal range of 13.0-18.0), white blood cell count was 13,600/mm$^3$ (normal range 4000-11,000), platelet count was 365,000/µL (normal range 150,000-450,000), neutrophils accounted for 74.8% (normal range 50-70%), lymphocytes were at 8.92% (normal range 20-40%), creatinine level was 0.9 mg/dL (normal range 0.5-1.3), and urea level was 89 mg/dL (normal range 10-60). No serological indications of hepatitis B or hepatitis C were found.

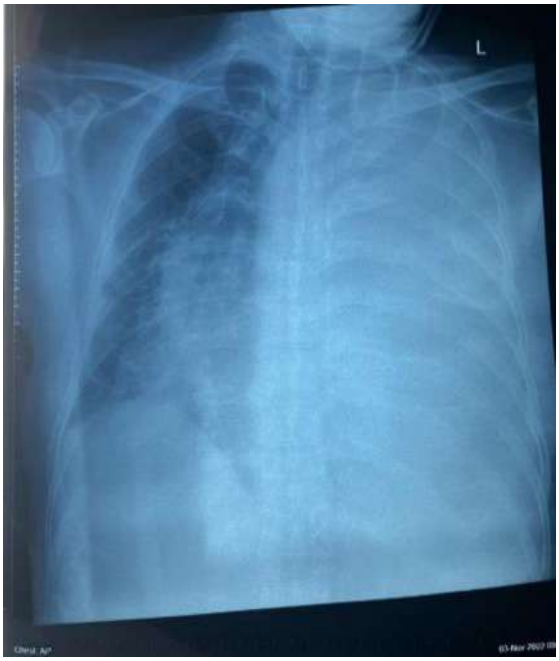


Figure 1. The anterior chest radiograph demonstrates a large left-sided pleural effusion extending into the left upper zone, causing contralateral tracheal deviation and mediastinal shift.

The chest X-ray (CXR) revealed a significant accumulation of fluid in the left pleural area that extended into the upper

portion of the left lung (Figure 1). Fluid accumulation caused a right-sided tracheal and mediastinal shift.

The results of the patient's physical examination were as follows: blood pressure (BP): 90/60 mmHg, heart rate (HR): 98x/min, respiratory rate (RR): 36x/min, temperature (T): 36.5°C, and $SpO_2$: 92%. Further physical examination showed chest wall expansion, abdominal breathing, face, and neck swelling, discoloration, and distended veins. Percussion on the left side of the chest indicated a dull sound, and auscultation revealed significantly reduced airflow at the lower part of the left lung. The patient's heart sounds were within the normal range, and he also exhibited leg swelling.

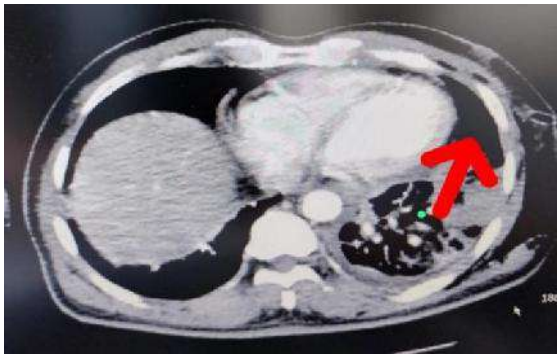

Figure 2. CT pulmonary angiogram in axial soft tissue windowing. Arrows indicate the presence of fluid. There was a left hydropneumothorax and atelectasis of the left lung, accompanied by a multifocal picture of diffuse mixed ground glass opacities (GGO) consolidation of the left lung, suspected pneumonia, and pulmonary tuberculosis (TB).

After being transferred to a more comprehensive medical facility, a multislice spiral computed tomography (MSCT) pulmonary scan was conducted. The MSCT scan showed multiple areas of diffuse, hazy lung opacity on the left side, indicating suspicion of tuberculosis and pneumonia.

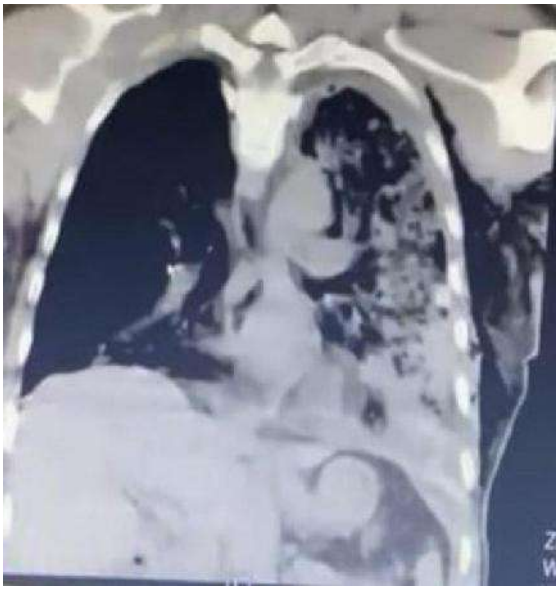

Figure 3. CT pulmonary angiogram in the coronal plane. A chest tube was installed in the left anterolateral 5-6th intracostal with a tip in the left pleural cavity.

An urgent MSCT pulmonary scan was requested to assess the characteristics and extent of the pleural effusion before proceeding with any interventions. The aim was also to rule out the possibility of a pulmonary embolism, as shown in Figures 2, 3, and 4.

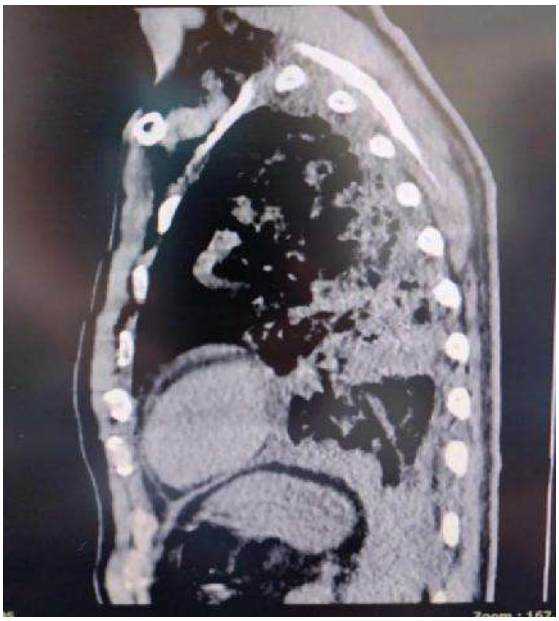

Figure 4. CT pulmonary angiogram in the sagittal plane. Subcutaneous emphysema was seen in the subcutaneous left anterolateral hemithorax.

Additionally, an echocardiogram revealed a considerable left-sided pleural effusion that led to the displacement of the left atrium and left ventricle, ultimately resulting in obstructive shock. The pleural fluid analysis was not performed on this patient.

Upon arrival, the patient displayed significant hemodynamic instability. Immediate measures involved administering oxygen through a non-rebreathing mask (NRBM)to achieve a target oxygen saturation level above 96%.

Additionally, the patient required two vasopressors (dopamine at a rate of 2.5 mcg/kg per minute of body weight and norepinephrine at a rate of 0.1 mcg/kg per minute of body weight) to sustain a blood pressure reading of 90/60 mmHg. A Foley catheter was inserted to monitor urine output. Given the patient's unstable hemodynamic condition and imminent death threat, urgent intervention was deemed necessary to alleviate the obstructive shock. A surgical consultation was conducted over the phone.

Thoracentesis (pleural drainage) was considered a potential therapeutic approach. This procedure involves removing more significant quantities of pleural fluid to relieve breathing difficulties caused by substantial pleural effusion. For individuals with new pleural effusions, a diagnostic thoracentesis is usually recommended.[8]

In the surgical theatre, a chest tube was placed on the left side to address the extensive accumulation of blood within the chest cavity. This procedure resulted in the drainage of approximately 1.5 liters of blood. The patient was given additional oxygen support, antibiotics, and furosemide. As a general recommendation, antibiotics from the quinolone generation are often preferred.

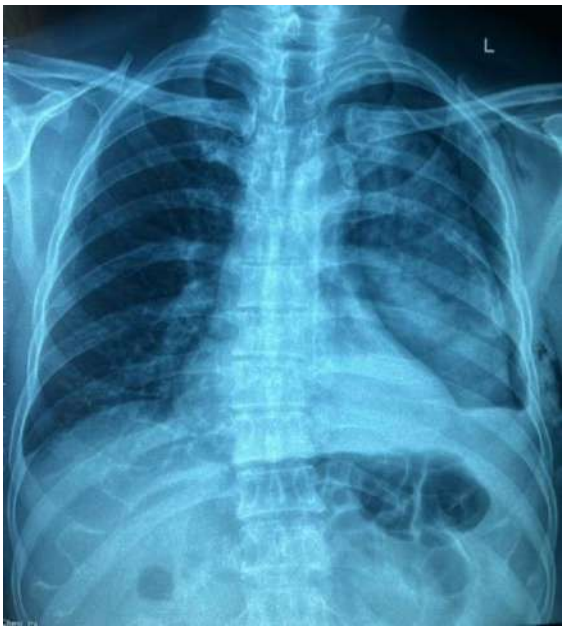


Figure 5. AP erect chest radiograph following left-sided thoracocentesis. This demonstrates almost complete resolution of the left-sided pleural effusion, with minimal residual fluid within the left costophrenic recess.

A subsequent chest X-ray (depicted in Figure 5) conducted the next day indicated significant improvement in the left pleural effusion, almost reaching full resolution after removing the chest tube. The initial mediastinal shift had also been resolved. With the patient's condition stabilizing, the patient was transferred to a more comprehensive medical facility for a CT pulmonary angiogram.

## DISCUSSION

The significance of urgent intervention in cases of obstructive shock occurring in patients with a substantial left-

sided pleural effusion. A pleural effusion, marked by an atypical fluid buildup in the pleural space caused by excessive production of fluid or compromised absorption, is commonly seen in pleural disorders.

Following tuberculosis (TB) treatment, the patient's condition improved notably. The initial rapid breathing rate of 30 breaths per minute has now returned to the normal range of 20-24 breaths per minute, and the initial body weight of 45 kg has increased to 52 kg.

A growing amount of fluid accumulating within the pleural cavity can decrease lung capacity, contributing to rapid breathing and lowered oxygen levels. If left unaddressed, the rising pressure within the chest could lead to diminished venous blood flow and compression of the right ventricle, presenting as low blood pressure.[3,9] In regions where TB is prevalent, the pleural variant emerges as the primary origin of pleural effusion. This statement underscores the importance of considering this diagnosis for all individuals experiencing pleuritic symptoms of unknown origin.[10]

Hemorrhaging into the pleural cavity can occur due to various disturbances affecting the chest wall tissues, pleura, or structures within the chest. The physiological reaction to the occurrence of a hemothorax becomes evident in two significant domains: hemodynamic and respiration. The extent of the hemodynamic reaction is contingent upon the volume and speed of blood loss.[11]

Hemodynamic alterations differ based on the bleeding volume and the speed at which blood loss occurs. A blood loss of up to 750 mL in an individual weighing 70 kg typically does not lead to noteworthy hemodynamic shifts. In the same person, a loss of 750-1500 mL results in the initial signs of shock, including rapid heart rate, accelerated breathing, and a decrease in pulse pressure.[12]

Signs of shock accompanied by inadequate tissue perfusion arise with a blood volume loss of 30% or more (approximately 1500-2000 mL). Given that the pleural cavity in a 70-kg individual can accommodate 4 L or more of blood, a severe hemorrhage can transpire without visible external evidence of blood loss.[13]

A substantial buildup of blood in the pleural cavity can impede the regular movement involved in breathing. In trauma, this can lead to disruptions in ventilation and the intake of oxygen, particularly when coupled with injuries to the chest wall.[8,14]

When a considerable amount of blood accumulates, individuals often encounter difficulty breathing, leading to the observation of rapid breathing, known as tachypnea. The quantity of blood needed to evoke these symptoms varies according to multiple factors, such as the specific organs affected, the extent of the injury, and the individual's existing pulmonary and cardiac capacity.[14]

Distinguishing a hemothorax from other effusions containing blood can be achieved by conducting a pleural fluid hematocrit test. A pleural fluid hematocrit

value exceeding 50% of the patient's peripheral blood hematocrit indicates a hemothorax.[11]

In both cases of cardiogenic and obstructive shock, patients usually exhibit indications of reduced cardiac output, such as cool extremities and weak pulses. They also display symptoms indicating elevated filling pressures in the LV or the RV, such as pulmonary edema, peripheral edema, and distended jugular veins.[15,16]

Within the unaffected and unscarred pleural space, a hemothorax is observed as a fluid meniscus obscuring the costophrenic angle or the surface of the diaphragm. This fluid also follows the pleural margins along the chest wall when visualized on an upright CXR. This radiographic presentation is analogous to what is seen with any other type of pleural effusion.[14,17]

Once a pleural effusion is confirmed, the underlying cause should be determined. Approaches for diagnosis encompass percutaneous pleural biopsy, bronchoscopy, thoracoscopy, and open pleural biopsy. Nevertheless, in the Emergency Department (ED), thoracentesis and chest tube insertion are usually adequate for assessment and treatment.[8]

## CONCLUSION

The subsequent pleural drainage effectively removed larger quantities of pleural fluid, alleviating the breathing difficulties associated with a sizable pleural effusion.

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Literature Review

# Selective Beta-Blockers on Chronic Obstructive Pulmonary Disease: A Literature Review

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## Abstract

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are usually coexisting. While beta-blockers are the indispensable management of an array of cardiovascular diseases, inhaled beta-receptor agonists are the central treatment for COPD patients. This review aims to assess the effect of beta-blockers on exacerbation rate, mortality, and quality of life among the COPD population. After the search on Cochrane Library, Pubmed, and Scopus, 15 relevant full-text articles published between 2012 and 2022 were included. We compared selective beta-blockers versus either non-users or non-selective agents. The results showed that selective beta-blockers did not increase the mortality and exacerbation rate in the COPD population and evidence on health-related quality of life is still sparse. However, more RCTs should be carried out for more precise information.

**Keywords:** beta-blockers, COPD, COPD exacerbation, mortality, quality of life

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) are usually coexisting. While beta-blockers are the indispensable management of an array of cardiovascular diseases, inhaled beta-receptor agonists are the central treatment for COPD patients.[1] Hence, many physicians worry that the administration of beta-blocker may devastate the stable condition of COPD and this misconception may prevent patients from guideline-recommended treatment.

COPD, a progressive chronic obstructive pulmonary condition, is suspected in over-35-year-old heavy smokers who have chronic dyspnea, progressive limitation of physical activities, and chronic cough. COPD is diagnosed given the post-bronchodilator $FEV_1/FVC$ of under 0.7.[2]

The main risk factor of COPD is protracted smoking or other inhaled toxic substance exposure. The acute worsening

episodes of COPD symptoms are called exacerbations, which have negative repercussions on patients' quality of life and the disease prognosis.[2]

In 2019, 3.23 million patients died from COPD and the majority of them were under 70. Additionally, COPD results in a remarkable financial encumbrance due to reduced productivity, everyday management expenses, and costs for acute flare-ups.[3] According to the EPIC survey performed in nine countries in the Asia-Pacific region, when 112,330 households were screened, 4289 individuals had the diagnosis of COPD. The estimated prevalence was 6.2%, with 19.1% of severe disease. 50% of patients in this survey reported acute events during the previous year.[4]

Both COPD and its acute exacerbations cause great encumbrance for not only individual patients but also the community. Hence, the control of COPD including interfering with acute events, reducing mortality, protecting the residual lung function, and improving daily symptoms and quality of life is important.[5]

CVDs are the common comorbid condition of COPD.[6] COPD patients have a considerably higher risk of ischemic heart disease, heart failure, cardiac dysrhythmia, pulmonary hypertension, and peripheral arterial diseases compared to healthy individuals.[7]

The assumed mechanisms of the relationship between these two conditions are multifaceted. The first element is the common risk factors including cigarette consumption, sedentary lifestyle, unhealthy diet, and exposure to pollution.[8] Secondly, emphysema in COPD patients also plays an important role. Hyperinflation increases the pressure on the cardiac system, causes dysfunction of the right ventricle, reduces the left ventricular filling, and then decreases the cardiac output.[8,9]

Furthermore, hypoxemia, resulting from pulmonary hyperinflation, leads to vasoconstriction, vascular remodeling, and cardiac repolarization alteration. The consequences are arrhythmias and sudden cardiac death. Chronic pulmonary inflammation increases the inflammatory factors such as surfactant protein D, C-reactive protein, fibrinogen, IL-6, IL-8, and TNF-α in the systemic circulation. These factors result in arterial stiffness and CVD.[8,9]

CVD harms COPD progression and outcomes. CVD increases the rate of hospitalization, hospital length of stay, in-hospital death, and readmission rate among COPD patients.[8] COPD, in turn, worsens the stability of CVD. In the SUMMIT randomized clinical trial with 16,485 COPD patients, the risk of CVD acute events was remarkably higher 30 days after a COPD flare-up and stayed high for up to 1 year.[10] Due to the vicious cycle between these two conditions, the treatment of both diseases must be optimized.

There are two types of beta-blockers, non-selective and selective agents. Selective beta-blockers affect predominantly the beta-1 receptors in cardiac and kidney tissue to hinder the effect of epinephrine and norepinephrine.

Selective beta-blockers include Atenolol, Bisoprolol, Metoprolol, Nebivolol, Betaxolol, Esmolol, and Acebutolol.[11] Selective beta-blockers are central to the management of many CVDs such as heart failure, atrial fibrillation, or ischemic heart diseases.[12–14]

Regarding COPD, inhaled beta-receptor agonists affect beta-2 receptors, which are located predominantly in the airway smooth muscle, to reverse the contraction of these muscles in COPD individuals.[15] While selective beta-blockers and beta-2 receptor agonists affect different receptors in the heart and the lungs, medical staff are still afraid that the co-administration of selective beta-blockers may devastate the stable situation in COPD patients. Here, we retrieve and synthesize the evidence of the safety profile of selective beta-blockers on COPD patients during the previous decade.

## METHOD

Open-access full-text English articles of randomized control trials, non-randomized control trials, and observational studies published in peer-reviewed journals from 2012 to 2022 were searched in Cochrane Library, PubMed, and Scopus with the searching string of ("Cardio-selective beta-blockers OR Selective beta-1-blockers OR Atenolol OR Bisoprolol OR Metoprolol OR Nebivolol OR Betaxolol OR Esmolol OR Acebutolol) AND ("chronic obstructive pulmonary disease" OR "obstructive lung disease" OR "COPD"). The primary inclusion criteria were COPD patients who had exposure to selective beta-blockers compared to either no beta-blocker therapy or non-selective agents. The outcomes of interest were the rate of acute exacerbations, mortality, and quality of life.

Firstly, we screened the titles and abstracts for relevant studies and appropriate information. Then, the articles without open access were excluded. The open-access full-text versions were analyzed by a single investigator for appropriate methodology and eligibility criteria. The reference list of all studies was rechecked to eliminate duplications.

After the search and screening process, 15 articles were included. For each study, data were extracted on the name of authors, year of publication, country of origin, design, study period, sample size, age, type of beta-blockers, and outcomes. Trends of outcomes were summarized and highlighted to build the report and identify evidence gaps.

## RESULTS

The electronic search identified 107 records. After removing 11 duplications, 1 research protocol, and 80 papers with inappropriate research questions, design, and language, or no free full text, 15 articles were included. Of over 15 publications, 11 studies reported the mortality rate, 7 studies gave information about the rate of acute exacerbations and only 2 papers informed the quality of life.

Table 1. Study characteristics

| Author | Design and time range | Country and time range | Age range (years) | Population | Number of subjects | Intervention | Comparison | Outcome |
|---|---|---|---|---|---|---|---|---|
| Dransfield et al (2019) | • Prospective, doubled blinded<br>• RCT†<br>• May 2016 – March 2019 | The United States | • Range: 40–85<br>• Mean: 65.0±7.8 | COPD* patients/ moderate airflow limitation + increased AECOPD§ risk | • Treatment group: 268<br>• Control group: 246 | Extended-release Metoprolol | Placebo | The time until the first exacerbation |
| Ke et al (2016) | • RCT†<br>• Jan 2012 –<br>• Jan 2015 | China | Range: 48-74 | Inhospital patients with HF‡ + COPD* | • Treatment group: 60<br>• Control group: 60 | Bisoprolol fumarate + trimetazidine | • Standard therapy:<br>• HF‡: Low flow oxygen inhalation + inotropic agents + reduced cardiac stress<br>• COPD*: antibiotics, doxofylline and ambroxol | Health-related quality of life |
| He et al (2017) | • RCT†<br>• Jul 2013 – Jul 2014 | China | Range: 44-85 | AECOPD§ patients complicated with right HF‡ | • Treatment group: 50<br>• Control group: 50 | Metoprolol tartrate oral | COPD* standard treatment following GOLD‖ 2013 | AECOPD§ Mortality rate |
| Angeloni et al (2013) | • Prospective<br>• Cohort study<br>• Apr 2004 – Apr 2009 | Italy | Mean:<br>• Treatment group: 70±8<br>• Control group: 70±9 | COPD* patients undergoing coronary artery bypass grafting | • Treatment group: 104<br>• Control group: 104 | Selective beta-blockers (Atenolol, Bisoprolol, Metoprolol, Nebivolol) | No beta-blockers | AECOPD§ Overall mortality |

| Author | Design and time range | Country and time range | Age range (years) | Population | Number of subjects | Intervention | Comparison | Outcome |
|---|---|---|---|---|---|---|---|---|
| Zvizdic et al (2019) | • Prospective cohort study<br>• 12-month follow-up | Bosnia and Herzegovina | --- | COPD* patients | • Treatment group: 24<br>• Control group: 44 | Selective beta-blockers (Bisoprolol, Metoprolol, Nebivolol) | Verapamil and Digoxin | AECOPD§ |
| Karimi et al (2020) | • Prospective population-based cohort study<br>• Jan 1991 – Jan 2011 | Netherlands | Mean: 69.7±9.2 | COPD* patients with cardiovascular indication of beta-blockers | Total population: 1312 | Selective beta-blockers | No beta-blockers | AECOPD§ |
| Dong et al (2016) | • Retrospective cohort study<br>• 1994 - 2013 | The United States, Italy, Taiwan | Mean: 71 | COPD* patients who hospitalized for acute coronary syndrome | • Treatment group: 18406<br>• Control group: 4579 | Selective beta-blockers | Non-dihydro-pyridine calcium channel blocker | All-cause mortality |
| Su et al (2016) | • Retrospective population-based cohort study<br>• Jan 2000 – Dec 2009 | Taiwan | Median: 70 (20–101) | HF‡ and COPD* patients | Total population: 11558 | Bisoprolol, Metoprolol, Carvedilol | No beta-blocker | Mortality |
| Mentz et al (2013) | • Retrospective analysis with data from OPTIMIZE-HF<br>• 2003 - 2004 | The United States | Mean age of COPD* population: 73 (63–80) | COPD* patients with LVSD | COPD* population: 722 patients | Selective beta-blockers | No beta-blockers & non-selective beta-blockers | Mortality |

| Author | Design and time range | Country and time range | Age range (years) | Population | Number of subjects | Intervention | Comparison | Outcome |
|---|---|---|---|---|---|---|---|---|
| Kubota et al (2021) | • Retrospective analysis with data from the ASIAN-HF registry<br>• 2010 - 2015 | China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand | • Treatment group: 63.3±13.6,<br>• Control group: 66.8±12.7 | HF‡ and COPD* patients | • Total population: 412<br>• Treatment group: 149<br>• Control group: 139 | Selective beta-blockers (Bisoprolol, Metoprolol, Nebivolol) | No beta-blocker | All-cause mortality Cardiovascular mortality |
| Huang et al (2017) | • Population-based nested case-control study<br>• 1998 - 2010 | Taiwan | • Case group: 72.12±8.25<br>• Control group: 72.50±9.01 | COPD* patients | • Treatment group: 16067<br>• Control group: 55970 | Selective beta-blocker | No beta-blocker | AECOPD§ |
| Mentz et al (2013) | • Analysis with data from HF-ACTION<br>• 2003 - 2007 | The United States, Canada, France | Median: 64 (56–71) | HF‡ and COPD* patients with ejection fraction ≤35% | 249 | Selective beta-blocker | Non-selective beta-blocker | Mortality |
| Chung et al (2022) | • Retrospective cohort study<br>• Jan 2001 – Dec 2013 | Taiwan | • Treatment group: 70.7±11.8<br>• Control group: 70.7±22.7 | COPD* patients with myocardial infarction | • Treatment group:7247<br>• Control group:7542 | Selective beta-blocker | Non-selective beta-blocker | All-cause mortality |

| Author | Design and time range | Country and time range | Age range (years) | Population | Number of subjects | Intervention | Comparison | Outcome |
|---|---|---|---|---|---|---|---|---|
| Stefan et al (2012) | • Retrospective cohort study<br>• Jan 2006 – Dec 2007 | The United States | Median: 72 (64–94) | Ischemic heart disease, congestive HF‡ and hypertension patients hospitalized for AECOPD§ | • Treatment group:7639<br>• Control group:2431 | Selective beta-blocker | Non-selective beta-blocker | In-hospital mortality |
| Kubota et al (2015) | • Retrospective, non-randomized single center trial<br>• Jan 2009 – Dec 2012 | Japan | • Treatment group: 78.2±8.2<br>• Control group: 79.1±6.5 | COPD* patients hospitalized for acute decompensated HF‡ | • Bisoprolol group: 34<br>• Carvedilol group: 52<br>• No beta-blocker: 46 | Bisoprolol | Carvedilol | All-cause mortality |

Note: *: Chronic obstructive pulmonary disease; †: randomized controlled trial; ‡: heart failure, §: acute exacerbation of COPD; ||: global obstructive lung disease

The main characteristics of these studies are shown in Table 1. In this article, we compare the effect and safety of selective beta-blockers versus no beta-blocker therapy and non-selective agents.

Among 15 included studies, 11 compared selective beta-blockers with non-users. 7 citations reported the mortality rate, 6 conveyed the rate of acute events and only 2 discussed the quality of life.

The beta-blockers for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (BLOCK COPD trial) is a double-blind RCT, which assessed the risk exacerbations and mortality rate of Metoprolol in 532 COPD patients aged between 40 and 85 years who had moderate airflow limitation with increased risk of acute events at 26 medical centers in the United States from May 2016 to March 2019.[16]

In the intervention group, Metoprolol was prescribed with the initial dose of 50 mg per day for 42 days before being titrated to 25, 50, and 100 mg per day based on the heart rate, systolic blood pressure, $FEV_1$ and side effects of Metoprolol.[16]

After 336 days, patients in both arms were weaned off either Metoprolol or a placebo and followed until 378 days for any symptoms of Metoprolol withdrawal. As a result, 11 and 5 individuals died in Metoprolol and control groups, respectively, with unadjusted HR of 2.18 (95% CI=0.76–6.29) and adjusted HR of 2.13 (95% CI=0.69–6.42; P=0.14).[16]

Another double-blind RCT in China assessed the safety of Metoprolol Tartrate prescribed for 100 heart failure patients who were hospitalized for acute exacerbation of COPD. As many as 100 patients aged 44 to 95 years were randomly assigned to Metoprolol and standard treatment arms. The dose of Metoprolol was sequentially adjusted to 6.25 mg, 12.5 mg, and 25 mg twice a day. Although no value of P was demonstrated, the mortality rate in the Metoprolol arm (0.0%) was lower than the control one (4.3%).[17]

Angeloni et al assessed the prescription of beta-blockers in 104 COPD patients who underwent coronary artery bypass grafting compared with 104 patients receiving no beta-blocker therapy at one institute from April 2004 to April 2009.[18]

Beta-blockers included Atenolol, Bisoprolol, Metoprolol, or Nebivolol. While the 30-day and in-hospital mortality were similar in both groups, the overall mortality after 3 years of follow-up in the beta-blocker group (7.7%) was lower than the control group (18,3%) with the value of P=0.03. The death incidence of the intervention group was 3.02 deaths per 100 patient-year, half of the control one, 7.03 deaths per 100 patient-year, with a relative risk reduction of 57% (P=0.004).[18]

By retrieving five databases in the United States, Taiwan, and Italy, Dong et al recruited 22985 COPD patients hospitalized for acute coronary syndrome to evaluate the safety of selective beta-blockers (22985 patients) compared to non-dihydropyridine calcium channel blockers (4579 patients).[19] The all-cause

mortality crude HRs for selective agents compared to the control one were 0.73 (95% CI=0.65-0.83). Using the high-dimentional propensity score matching technique, the treatment group included 11497 patients and the control group comprised 3588 people with adjusted HRs were 0.90 (95% CI=0.78-1.02).

A nationwide retrospective population-based cohort study in Taiwan recruited 11558 COPD individuals who had concomitant heart failure from the Taiwan National Health Insurance Research Database between January 2000 and December 2009 to assess the survival effect of Bisoprolol, Metoprolol, and Carvedilol compared with no beta-blocker therapy. The defined daily doses of Carvedilol, Bisoprolol, and Metoprolol were 6.25 mg, 1.25 mg, and 25 mg in that order. The patient population was divided into two groups, heart failure with and without concomitant COPD.[20]

In the COPD subgroup, only Bisoprolol showed an association regarding survival effect compared with nonuse while no association between Carvedilol and Metoprolol was observed. The effect of low and high posology was also analyzed. Additionally, this effect was dependent on bisoprolol posology. Low-dose with HR=0.76 (95% CI=0.59–0.97; P=0.030) and high-dose with HR=0.40 (95% CI=0.26–0.63; P<0.001).[20]

Using data from the large national registry and the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) in the United States, Mentz et al performed a retrospective analysis of 722 COPD patients who had an ejection fraction of less than 40% to evaluate the safety of selective beta-blockers versus non-users in COPD population. The HR for 60-day mortality when comparing cardio-selective and no beta-blocker therapy was 0.53 (95% CI=0.25–1.13).[21]

Extracting data from the ASIAN-HF registry, a prospective observational multinational study performed in 11 Asian countries from 2010 to 2015, Kubota et al recruited 412 heart failure who had concomitant COPD and divided these patients into 3 groups regarding the type of beta-blocker: non-users (n=139), selective (n=149), and non-selective agents (n=124).[22]

Hence, all-cause mortality, cardiovascular mortality, and heart-failure-related rehospitalization were measured. Concerning all-cause mortality, the adjusted HR of selective beta-blockers compared with non-users was 0.58 (95% CI=0.34–0.99; P=0.044) while no association was observed before the adjustment (P=0.139). Furthermore, no association between cardio-selective agents and cardiovascular mortality.

In the previously mentioned BLOCK COPD trial, which compared Metoprolol and placebo on 532 COPD patients, no significant difference in the median time until the first exacerbation between the intervention and control groups with the unadjusted HR=1.05 (95% CI=0.84–1.32; P=0.66) and adjusted HR=1.12 (95% CI=0.88–1.42). While there was no difference in the overall rates of

exacerbations between the two groups with a rate ratio of 1.05 (95% CI=0.85–1.28), the rate of severe exacerbation and very severe exacerbation was higher in the Metoprolol group compared to the control arm, with the rate ratio of 1.51 (95% CI=1.00–2.29) and 3.71 (95% CI=1.10–16.98) respectively.[16]

The previously mentioned RCT in China by He et al also studied the effect of Metoprolol Tartrate on the frequency of acute COPD exacerbations among 100 heart failure patients hospitalized due to acute exacerbation of COPD between July 2013 and July 2014.[17] The exacerbation frequency of the Metoprolol arm (1.64±0.94 times/year) was significantly higher than the control arm (2.04±0.82 times/year; t= -2.215; P=0.029).

The prospective cohort study by Angeloni et al outlined in the previous part also reported the results on COPD exacerbations. As demonstrated in this study, the COPD exacerbation rate of the intervention group (Atenolol, Bisoprolol, Metoprolol, or Nebivolol) was similar to the control one (44.2% vs 43.3%; P=0.99).[18] The person-time incidence of the beta-blocker group was 17.4 events/100 patient-years versus 16.7 events/100 patients-years for the control population (4% relative risk increase; P=0.47).

In another prospective cohort study, Zvidic et al recruited 68 GOLD II-III COPD patients with a left ventricular ejection fraction of more than 35% and divided them into 2 groups of moderate (GOLD II) and severe (GOLD III) airflow obstruction given the spirometry results.[23]

In each group, the intervention arm was treated with Metoprolol, Bisoprolol, and Nebivolol while the control arm received Verapamil along with Digoxin. The follow-up period was 12 months and the endpoint was the frequency of exacerbations. As a result, the number of exacerbations of the experimental arm (0.600±0.632) was remarkably inferior to the control group (1.333±0.963) with the value of P=0.007) in the moderate airflow obstruction group while no statistical difference between the two arms was found in the severe airflow obstruction group.[23]

From the Rotterdam study, which is a prospective population-based cohort study in the Netherlands on 15000 participants, Karimi et al followed 1312 COPD subjects from January 1991 to January 2011 intending to evaluate the association between beta-blocker and COPD exacerbations in patients with and without cardiovascular indications for beta-blockers.[24]

In the total population of 1312 patients, the current use of selective agents decreases the risk of flare-ups compared with non-users (HR=0.69; 95% CI=0.58–0.83; P=0.00005). With subgroup analysis in patients with cardiovascular indication for beta-blockers, the current use of selective agent also reduced the number of COPD acute events compared to non-users (HR=0.69; 95% CI=0.57–0.85; P=0.0004) while this association was not proved in the group without cardiovascular indication for beta-blocker (HR=0.94; 95% CI=0.55–1.62; P=0.835).[24]

From 1998 to 2010, a population-based nested case-control study retrieved 16067 COPD patients with severe exacerbations and 55970 stable COPD patients from the Taiwan National Health Insurance Research Database as the case and the control groups to assess the safety of beta-blockers on COPD patients. The age, gender, COPD diagnosis period, and beta-blocker use duration were matched in both groups.[25]

What was observed, is that there was a lower risk of acute exacerbations in the current selective beta-blocker users compared with the non-users (OR=0.90; 95% CI=0.85–0.96). Among Acebutolol, Atenolol, Betaxolol, Bisoprolol, and Metoprolol, Betaxolol showed a significant reduction of acute exacerbation risk (OR=0.75; 95% CI=0.60–0.95) .[25]

Two studies reported the health-related quality of life and both studies used St. George's Respiratory Questionnaire. An RCT performed between January 2012 and January 2015 randomly recruited 120 patients aged 48 to 74 years to compare the combination of Bisoprolol and Trimetazidine with the standard treatment in grade II-III heart failure with comorbid COPD.[26]

The standard treatment included low-flow oxygen, inotropic agents, antibiotics, Doxofylline, and reduced cardiac stress therapy. Trimetazidine was given orally at 20 mg 3 times per day. The posology of Bisoprolol was increased gradually depending on the patient's tolerance.[26]

The results showed no statistical differences between the 2 groups with St. George's Respiratory Questionnaire total scores before treatment of 55±13 and 54±12 for the control and treatment groups respectively (P>0.05). However, after the treatment administration, the score of the treatment group (40±11) was significantly lower than the control group (54±12) with the value of P<0.05.[26]

Once again, the previously mentioned BLOCK COPD trial also showed no difference between the Metoprolol and placebo groups. However, no specific data were shown.[16]

Among 15 articles, 5 publications compared cardioselective versus non-selective agents. All 5 studies conveyed the mortality rate and only 1 study discussed the COPD exacerbation rate. No study gave information on the quality of life.

With the data from the OPTIMIZE-HF trial as mentioned above, Mentz et al performed a retrospective analysis in 722 COPD patients who had an ejection fraction of less than 40% to compare not only the selective beta-blockers versus non-users but also the selective versus non-selective agents. What is concluded, is that no significant difference was found regarding 60-day mortality with HR=1.14 (95% CI=0.57–1.56).[21]

With the data from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), which was a multicenter RCT in the United States, Canada, and France to evaluate the effect and safety of physical activity training in heart failure patients, Mentz et al identified

249 COPD patients aged 56 to 71 and performed an analysis to investigate the risk of mortality/hospitalization of beta-blocker use.[27] In this COPD cohort, no evidence for the association of beta-blocker types and risk of mortality/hospitalization was found with an adjusted HR=0.91 (95% CI=0.64–1.29; P=0.58).

More recently, a retrospective nationwide population-based cohort study enrolled 7247 patients using selective beta-blockers and 7542 patients on non-selective agents from the Taiwan National Health Insurance Research Database to compare 2 types of beta-blockers on COPD patients who had a comorbid myocardial infarction. Patients were followed every 3 months until withdrawal, death, or December 2013.[28]

All-cause mortality and major adverse cardiac and cerebrovascular events were the outcomes of interest. In terms of mortality, the results showed that the selective agents showed a superior safety profile than the non-selective one after the inverse probability of treatment weighting (8.9 vs 9.6 events per 100 person-years; HR=0.93; 95% CI=0.89–0.96). With subgroup analysis, Bisoprolol was better than Carvedilol (9.3 vs 10.3 events per 100 person-years, HR=0.90; 95% CI=0.86–0.94).[28]

As many as 7639 and 2431 COPD patients receiving selective and non-selective beta-blockers for ischemic heart disease, congestive heart failure, and hypertension were retrieved from the Perspective inpatient administrative database and included in a retrospective cohort study from 1 January 2016 to 1 December 2017.[29]

The outcomes included in-hospital mortality, late mechanical ventilation, hospital length of stay, and 30-day readmission. Metoprolol (74%) and Atenolol (23.5%) were the most common selective agents prescribed while Carvedilol (85%) and Propranolol (7.2%) were most indicated as non-selective medications. After matching by propensity score adjustment, there was no association between the selectivity of beta-blockers and in-hospital mortality with OR=0.88 (95% CI=0.71–1.09).[29]

Kubota et al conducted a retrospective, non-randomized, single-center trial from 1 January 2009, to 31 December 2012 on 132 COPD patients hospitalized for acute decompensated heart failure.[22]

At discharge, 46 patients received no beta-blockers, 52 patients received Carvedilol, 34 patients received Bisoprolol, and all of them were followed every 1-2 months. When comparing Carvedilol and Bisoprolol, no difference in all-cause mortality rate was found (11.5% and 8.8%, correspondingly).[22]

Also, in the retrospective, non-randomized, single-center trial by Kubota et al in 2015 on 132 COPD and heart failure patients, Carvedilol, a non-selective agent, demonstrated a higher rate of acute exacerbations of either heart failure or COPD than Bisoprolol (55.8% vs 17.6% respectively; P=0.033).[22] It concluded that Bisoprolol was safer than Carvedilol.

## DISCUSSION

COPD, which results from bronchitis with/without emphysema, is diagnosed given the exposure to risk factors, appropriate clinical findings, and spirometry results.[2] It is well established that CVDs are a prevalent comorbid disease in COPD patients.[6,7] While inhaled beta-agonists are the main medication for COPD patients,[2] beta-blockers are the hallmark of the treatment for many CVDs.[1]

Medical staff worldwide are concerned that the treatment of beta-blockers may devastate the stable condition of COPD. Hence, we aim to summarize the evidence available during the last decade about the safety of selective beta-blockers on COPD patients focusing on 3 outcomes including mortality, acute exacerbation, and quality of life. Primarily, we intended to include only RCTs but after the preliminary database search, only 3 RCTs during the previous decade were found. Hence, we included all study types including randomized control trials, non-randomized control trials, and different types of observational studies. As a result, 15 studies were identified and most were cohort studies.

Firstly, we aim to compare selective beta-blocker versus no beta-blocker therapy. Among 7 studies that compared the mortality rate between the 2 groups, 3 studies concluded that the mortality rate was similar, and 4 studies reported that selective agents decrease the risk of death in COPD patients. In other words, selective beta-blockers did not increase the mortality rate in COPD patients. Among 6 studies that gave information on COPD acute exacerbation, 2 showed similar results between groups, 3 indicated that selective agents could reduce the risk of exacerbations and 1 reported that the risk of exacerbation was related to the severity of airflow limitation. To clarify, the risk of COPD acute events does not increase when patients are prescribed selective beta-blockers.

The mortality and acute exacerbation safety of beta-blockers in COPD patients have been proven in some previous systematic reviews and meta-analyses. A systematic review and meta-analysis by Etminan et al included 9 retrospective cohort studies from 1961 to 2012 to clarify this safety.[30]

Although there were biases and heterogeneity between studies, the protective effect on all-cause mortality was demonstrated with a pooled relative risk of 0.69 (95% CI=0.62–0.78; I2=82%). This study is different from ours because there was no selectivity of beta-blockers. Another meta-analysis by Du et al with 15 cohort studies published between 1966 and 2013 showed the reduction of overall mortality (relative risk of 0.72 with 95% CI=0.63–0.83) and COPD exacerbation (relative risk of 0.63 with 95% CI of 0.57 – 0.71) in the beta-blocker group.[31]

However, like the previous one, this meta-analysis included both selective and non-selective medications in the intervention group, which is different from our review. More recently, Gulea et al included 23 observational studies and 14

RCTs. In terms of COPD exacerbation, only 1 RCT and 5 observational studies were identified and included.[32]

The result is that the risk of COPD flare-up is reduced with the presence of beta-blockers (HR=0.78; 95% CI=0.74–0.82). With respect to mortality, the narrative syntheses showed the adjusted risk estimates between beta-blocker versus no beta-blocker therapy were from HR was 0.46 (95% CI=0.19–1.11) to 1.19 (95% CI=1.04–1.37). Hence, beta-blockers did not have a detrimental effect on the COPD population. Again, this meta-analysis assessed both selective and non-selective agents.

Therefore, we further our review and compare selective and non-selective agents. In terms of mortality, 4 studies showed no difference between 2 agents and only 1 paper reported the superior effect of selective medication. Regarding exacerbation rate, only one publication was available and the sample size was relatively small (132 patients). In most of these studies, the superior effect of selective beta-blockers in the COPD population was not concluded but the number of studies was relatively small and there was a lack of RCTs, which are the best design in the hierarchy of evidence.

Additionally, we identify some gaps that can be filled by further research. Firstly, an array of observational studies concerning the utilization of beta-blockers in the COPD population were published but high-quality RCTs and related systematic reviews and meta-analyses are still sparse. Secondly, the evidence on quality of life was still limited. There were only 2 RCTs that compared the St. George's Respiratory Questionnaire between selective beta-blockers and non-users during the last 10 years and the results were contradictory. Hence, more well-designed research should be conducted to fill in these gaps.

## CONCLUSION

This review shows that the use of selective beta-blockers among COPD patients is safe because these medications do not increase death and COPD exacerbation. However, there should be more double-blind RCTs with appropriate sample sizes to critically examine this safety. Furthermore, we are unable to establish the superior safety of selective beta-blockers compared with non-selective agents because the evidence with high-quality methodological design on this question is still sparse. Ultimately, the evidence on health-related quality of life is limited and more research is needed to shed light on this problem.

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Literature Review

# Current Knowledge of Mycobacterium Other Than Tuberculosis (MOTT) in this Current Era: Definition, Taxonomy, and Diagnose

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## Abstract

Globally, Pulmonary Tuberculosis (PTB) remains a health concern, with an annual increase in cases. Indonesia is the second-highest contributor to PTB cases globally, below India, which also saw an increase in cases, particularly after the COVID-19 pandemic. Nontuberculous Mycobacteria (NTM) infections contribute to the increase in PTB cases through misdiagnosis and overlapping conditions. The occurrence of changes in the composition of NTM species in the Mycobacterium genus is the premise for updating the diagnosis of NTM with several supporting examination modalities. Clinical, radiological, and microbiological criteria have been established by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) for the diagnosis of NTM. The relationship between these three criteria is essential as a guideline for distinguishing infections caused by Mycobacterium tuberculosis (Mtb) from those caused by NTM.

**Keywords:** NTM, MOTT, pulmonary tuberculosis

## INTRODUCTION

Pulmonary tuberculosis (PTB) is still a global health concern and one of the main infectious causes of mortality, second only to HIV/AIDS. According to the World Health Organization (WHO), in 2022, nearly 90 percent of the incidence of PTB increased significantly from 2019 to 2021, with Indonesia contributing the second-most PTB cases in the world.[1]

As one of the endemic countries, the handling of PTB cases in Indonesia is a priority of the government program to take on case finding as the first step in preventing the spread of active PTB infection in the community. So that there is no underdiagnosis or overlapping between Mycobacterium tuberculosis (Mtb) and Nontuberculous Mycobacteria (NTM) infections, the rapidity and accuracy of the diagnosis of PTB requires consideration of the results of microscopic examination.[1,2]

Pulmonary tuberculosis is a contagious infectious disease microscopically induced by the Mtb complex. *M. tuberculosis*, *M. bovis*, *M.*

*caprae, M. africanum, M. microti, M. canneti* and *M. pinnipedii* make up the Mtb complex group.[2] Based on the National Tuberculosis Control Guidelines, PTB is typically caused by infection with *M. tuberculosis, M. africanum, M. bovis and M. leprae*. Several studies have been conducted to identify additional Mycobacterium species that can induce PTB infection, also known as Mycobacterium Other Than Tuberculosis (MOTT).[2,3]

In countries that are developing, determining and identifying MOTT infection is difficult due to the lack of clinical findings and laboratory diagnostic tools. Typically, the clinical manifestations of MOTT infection are non-specific. Moreover, radiological and clinical characteristics share similarities with PTB. MOTT-infected patients with positive culture results are frequently regarded as contamination and, in some instances, are designated as clinical PTB and given antituberculosis drugs (ATD) without progressive clinical evaluation.[4]

## TAXONOMY OF MYCOBACTERIUM

In 1896, which was Lehmann and Neumann in Germany introduced the genus Mycobacterium, which has been identified as class Actinomycetes, ordo Actinomycetes, family Mycobacteriaceae, genus Mycobacterium. In concert with the development of phenotyping techniques, the taxonomy of Mycobacterium has been modified by employing phylogenomic analysis. There are 190 species in the genus Mycobacterium and the pathogens are Mtb and *M. leprae*.[5]

The MOTT terminology was superseded by the term NTM Lung Disease in the Tuberculosis Physician Manual Pulmonary in 2022. NTM refers to subspecies of Mycobacterium other than Mtb complex and *M. leprae*. The majority of the 150 species in the NTM classification are nonpathogenic.[6]

Infections caused by NTM are frequently associated with contamination processes in the surrounding environment, with unknown transmission routes. Based on a study conducted by Morimoto et al., NTM infection or reinfection in humans is caused by the same genotype and is transmitted through the air. In addition, the sampling procedure can alter the microscopic results of the Mycobacterium genus, according to the study.[7]

The examination of NTM growth in cultures reveals two distinct processes. First, species can develop rapidly in cultures lasting 7 to 10 days. *M. abscessus complex, M. chelonae, M. fortuitum,* and *M. mucogenicum* are the different varieties of Mycobacterium species. The second process is slow growth with a culture duration of >14 days. Included in this category of Mycobacterium species are *M. avium complex* (MAC), *M. chimaera* and *M. kansasii*. *M. avium* and *M. intercelullare sp* are MAC group members.[8]

The identification approach of NTM is utilized for accurate diagnosis and treatment. *M. gordonae*, for instance, is a species that rarely causes clinical manifestations and does not necessitate

treatment despite its detection via culture examination. Other species, such as MAC, *M. kansasii*, and *M. abscessus* can induce pulmonary infections and are pathogenic. As described in Table 1, the infection process of NTM involves the lymphatic system, skin and soft tissues.[6,9,10] There are significant microscopical differences between Mtb and NTM, such as the positivity value on the Acid-Fast Bacilli (AFB) examination.[9]

Table 1. Description and Predilection of Pathogenic NTM[6,10,11]

| Organism | Predilection | Description |
|---|---|---|
| *M. avium complex (MAC)* | • Lung<br>• Lymphatics | • Existing in all environments.<br>• Lady Windermere Syndrome is prevalent in HIV-infected and elderly individuals, particularly women. |
| *M. xenopi* | Lung | Frequently observed in GERD patients |
| *M. abscessus complex* | Lung | • Pathogenic.<br>• Resistant to macrolide antibiotics. |
| *M. kansasii* | Lung | • Usually found in water pipes.<br>• Adults and the elderly with a history of COPD are frequently infected. |
| *M. fortuitum* | • Lung<br>• Skin<br>• Soft tissue | Typically nonpathogenic, but can cause nosocomial infections. |
| *M. marinum* | • Skin<br>• Soft tissue | • Forms granulomas in fish tank or pool water (Fish Fancier's Finger).<br>• Capable of surviving and reproducing at temperatures between 27° and 37°C. |
| *M. ulcerans* | • Skin<br>• Infections in incisions caused by mycolactone toxin trauma, that include nodule-like, asymptomatic skin efflorescence and ulcers | • Prevalent in subtropical and tropical zones.<br>• Increases throughout the rainy season and flooding.<br>• Children and young adults are frequently affected. |
| *M. decipiens* | • Skin lesions<br>• Lymph nodes | Resulting in synovitis and lymphadenitis |
| *M. shigaense* | • Skin<br>• Lung<br>• Lymph nodes | Possible outcomes include lung infection, cutaneous infection, and widespread infection. |

## DIAGNOSIS

The diagnosis of NTM infection remains difficult for all medical professionals. According to the ATS/IDSA, the interaction between clinical, radiological, and microbiological criteria can serve as a diagnostic strategy. As radiologic indicators, X-ray examination and High-Resolution Computed Tomography (HRCT) are utilized. While microbiological criteria can be determined through Bronchial Alveolar Lavage (BAL) or sputum examination at two distinct times, BAL examination is preferred.[12]

### Clinical Criteria

Based on its location, the symptoms of NTM infection are divided into Pulmonary NTM and Extrapulmonary NTM. Pulmonary NTM manifestations differ considerably and depend on the severity of infection and other underlying diseases. Pulmonary NTM infection shares clinical similarities with PTB infection, including hemoptysis, shortness of breath, lethargy, and weight loss. However, other symptoms such as fever and nighttime perspiration are uncommon in Pulmonary NTM infection.[6]

The clinical criteria for Pulmonary NTM consist of:[6]

1. NTM due to other underlying diseases
   a. Bronchiectasis, cystic fibrosis, COPD, and pulmonary tuberculosis are the underlying diseases.
   b. These characteristics are frequently infected by the pathogens MAC, *M. abscessus* and *M. kansasii*.
2. NTM without other underlying disease
   a. The majority of clinical manifestations occur in nonsmoking women >50 years without underlying pulmonary disease.
   b. Progressive cough and persistent shortness of breath are the presenting symptoms.

Based on study results conducted by Lee et al, the prevalence of pulmonary NTM was 58.8% and that of extrapulmonary NTM was 41.2%. The highest incidence of extrapulmonary NTM 35.3%, was found in lymph nodes, followed by skin, lymph nodes and soft tissue.[12] The clinical manifestations of Extrapulmonary NTM infection are frequently found in patients with HIV/AIDS, a history of immunosuppressant drugs, cancer, and organ transplantation.[13]

### Radiologic Criteria

The radiologic examination is one of the modalities of diagnosis of Pulmonary NTM infection. Pulmonary NTM radiologic characteristics are also highly variable and difficult to distinguish from PTB. The recommended radiologic tests are X-ray and HRCT.[6,14,15]

Radiologic criteria are two types, there are:[6]

1. Features of Fibrocavities
   a. The radiologic characteristics are comparable to post-infection PTB.
   b. Most of the lesions are located in the superior lobe.
   c. Frequent complications include progressive fibrosis, atelectasis, and traction bronchiectasis.

d. Other characteristics include heterogeneous linear and nodular opacities with or without calcification.

2. Features of Nodular Bronchiectasis
   a. There is multifocal cylindrical bronchiectasis and 1-3 mm centrilobular nodules described as "*Tree in bud opacities*." Frequently observed in patients with NTM and no underlying disease.
   b. It is frequently discovered in the middle lobe of the right lung.
   c. It is known as the "Lady Windermere Syndrome" and is more prevalent in elderly women.

The species of Mycobacterium that causes pulmonary NTM infection may exhibit certain radiological characteristics, but these characteristics are not considered pathognomonic. Some HRCT images of Mycobacterium species are presented below.

Based on the research conducted by Lee et al, patients with the underlying disease have a significant amount of nodules and opacities measuring >2 cm in diameter, with or without cavities described as "ill-defined nodules". Statistically, there was no significant difference between immunosuppressants and immunocompromised, according to the study's findings, which indicated that the immunocompromised control group differed only in the appearance of poorly defined nodules.[16]

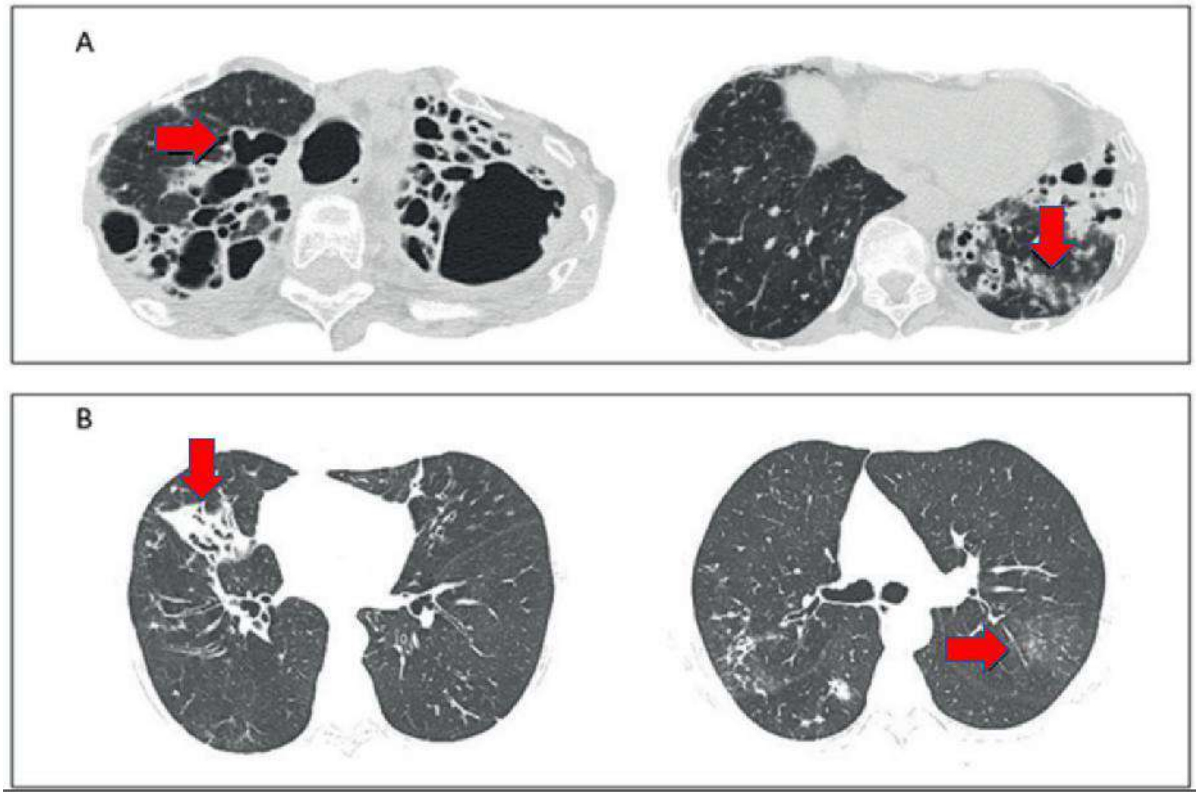


Figure 1. (A) CT scan of an immunocompromised patient infected with *M. asiaticum*; extensive varicose bronchiectasis and parietal bronchial hypertrophy. Centrilobular opacity with characteristics of ground glass. (B) CT scan of a patient infected with *M. avium-intercellulare*; the middle lobe underwent consolidation. Middle lobe and lingual region dominant bronchiectasis with characteristics of ground glass, centrilobular opacity[17]

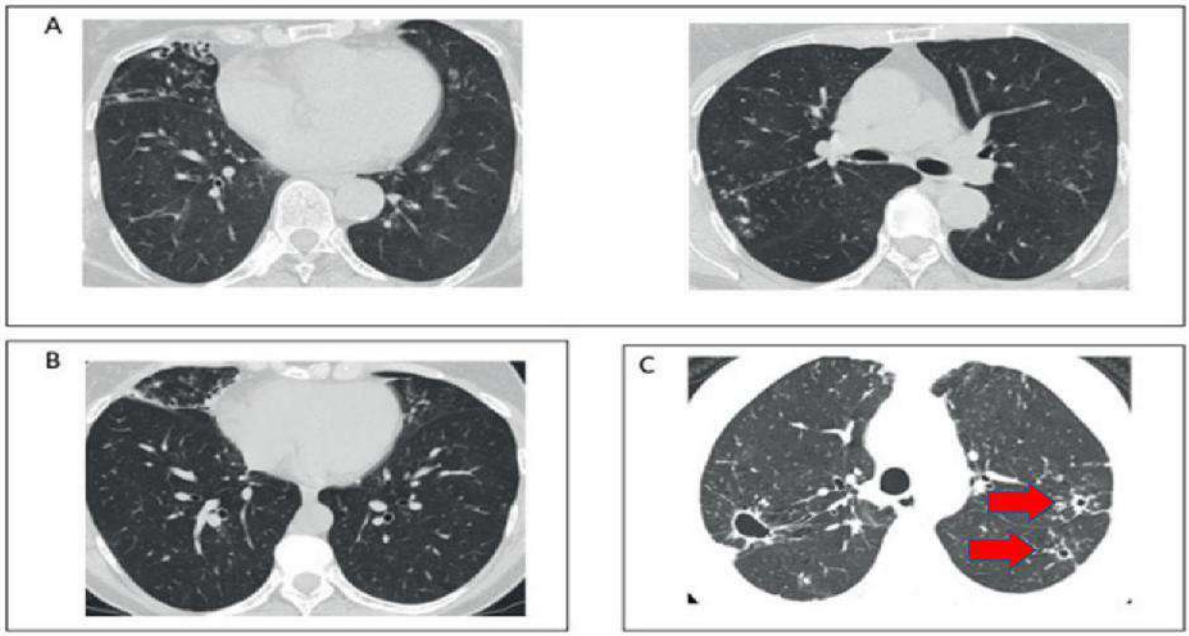


Figure 2. (A) A CT scan of a patient infected with *M. fortuitum*; middle lobe bronchiectasis with micronodules in the right upper lobe. (B) A CT scan of a patient infected with *M. Intercelulare*: middle lobe and lingula bronchiectasis with micronodules. (C) Cavities with solid walls in the upper lobe, micronodules in the centrilobular and "*tree in the bud*" in the left upper lobe[17]

Fowler et al conducted a cohort study in which culture-positive NTM patients were compared with culture-negative NTM patients and HRCT examination and scoring was performed. The research revealed that there was no significant difference between the two groups' scores.[15]

Based on a study by Bonnet et al, 2/3 of Pulmonary NTM patients show fibrocavities with bronchiectasis of as much as 60% and cavities as high as 40%. These findings suggest that former PTB patients who will develop a post-inflammatory bronchiectasis picture will face similar radiological challenges. From the above studies, it can be concluded that there is no specific picture for Pulmonary NTM infection, but the results can explain that the predilection of lesions that appear on radiology is in the middle lobe and lingula location.[18,19]

**Microbiological Criteria**

The majority of Mycobacterium included in the NTM group are nonpathogenic, so sputum examination is continued in the microbiological examination. Patients with clinical non-productive cough may be recommended bronchoscopy as an alternative to radiological images of nodular bronchiectasis for sample collection, as it is considered to have high sensitivity. Sputum induction can be given N-acetylcysteine but has the potential to result in contamination of the results thus affecting the viability of Mycobacterium.[8,20]

Based on the Clinical Laboratory Standards Institute, chlorhexidine can be used as another alternative in sputum induction without disturbing Mycobacterium viability. A study conducted at the Department of Microbiology, Faculty of Medicine, University of Indonesia also

indicates that the use of N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH) for sputum induction has a high contamination rate of Mycobacterium culture examination results, resulting in a lower rate of Mycobacterium positivity.[6,21,22]

### 1. Acid Fast Bacilli (AFB)

The morphology of Mycobacterium species is "*Acid-fast*" and mycolic acid is a long-chain fatty acid (C60 - C90) that is linked to arabinogalactan via glycolipid bonds and to peptidoglycan via phosphodiester bridges. So that Mtb can withstand acid alcohols and carbol fuchsin, the cell wall is composed of mycobacterial sulfolipids and polysaccharides such as arabinogalactan and arabinomannan.[23] In NTM, the sensitivity of BTA examination is considered to be low, leading to the use of additional examination modalities. Some AFB stains can be seen in Table 2.

### 2. Molecular Method

Molecular methods based on (1) Phenotyping and biochemical characteristics, (2) Genomics, (3) DNA Probe Assay, (4) Species-specific PCR Detection of Mycobacterium, and (5) Whole Genome Sequencing can be used to identify Mycobacterium species.[24]

In-vitro amplification of Deoxyribo Nucleic Acid (DNA) or Ribo Nucleic Acid (RNA) chains is used to evaluate the phenotype of NTM. This method is the basis for conventional Polymerase Chain Reaction (PCR), real-time PCR, PCR restriction fragment length polymorphism analysis, oligonucleotide array and sequencing.[20,25]

Table 4. Type of Sputum Staining[21]

| Type of Staining | Description |
|---|---|
| Ziehl Neelsen | • All specimen<br>• Result: bright red with blue background<br>• For all *Mycobacterium* |
| Kinyoun | • Requires a systopin or a solid culture medium<br>• Result: bright red<br>• Species that can be detected: *M. fortuitum, M. chelonae, M. abscessus,* MAC |
| Rapid Modified Auramine O Fluorescent | • All specimen<br>• Result: orange-yellow or light green with a dark background<br>• No coloring occurred on Mycobacterium-rapid grow |
| Fite (Gomori-methenamine Silver Stain) | • The specimen was taken from the soft tissue<br>• Result: Pink with blue background<br>• *M. Leprae* detected |
| Periodic Acid Schiff (PAS) Stain | • The specimen was taken from the soft tissue<br>• Result: Pink<br>• *M. kansasii,* MAC, *M. ulcerans, M. Chelonei* |

There are a few methods that can be used, such as:

***a. PCR***

Gene-Xpert MTB/RIF was developed by the WHO to detect Mtb and Rifampicin resistance via the Nucleic Acid Amplification Technique (NAAT). This test is an example of real-time PCR, which gives results within 2 hours.[26] Positive AFB and Gene-Xpert test results can be used as evidence for an NTM infection suspicion. These two tests can enhance the diagnosis, with a sensitivity of 87% for distinguishing Mtb from MAC.[6]

The Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) recommend the use of Gene-Xpert with a positive AFB result as the initial step in the diagnosis of NTM:

Table 5. Diagnosis of Mycobacterium based on AFB and Gene-Xpert[4]

| Sputum AFB | Sputum Gene-Xpert | Interpretation |
|---|---|---|
| Positive | Positive | Mtb |
| Positive | Negative | Suspect of NTM |
| Negative | Positive | Mtb |
| Negative | Negative | Suspect of non infection |

***b. DNA Probe Assay***

*Accu-probe* (Gen-Probe) was the first DNA probe developed to identify Mycobacterium. This Mycobacterium identification test has limitations, as it can only detect *Mtb complex, M. avium complex, M. kansasii,* and *M. gordonae*.[24]

Line Probe Assay (LPA) was created from the DNA Probe assay of the first generation. LPA examination is comprised of two types: The first, Inno LiPA Mycobacterium V2 which detects and identifies the genus Mycobacterium and 16 other Mycobacterium species based on 16S-23S rRNA, including Mtb complex*, M. avium, M. intracellulare, M. scrofulaceum, M. kansasii, M. xenopi, M. chelonae, M. gordonae, M. fortuitum complex, M. malmoense, M. genavense, M. simiae, M. smegmatis, M. haemophilum, M. marinum/M. ulcerans* dan *M. celatum*.[24]

The second type of LPA test is the GenoType Mycobacterium assay, which is used to distinguish between Mtb based on *gyrB gene polymorphism.* GenoType *Mycobacterium* CM (*Common Mycobacteria)* stimulates the Mtb molecule and 24 NTM species, whereas GenoType Mycobacterium AS (additional species) stimulates the identification of 19 NTM species.[24]

***c. Loop-Mediated Isothermal Amplification (LAMP)***

The LAMP method was created by amplifying DNA polymerase to recognize 6 DNA sequencing. LAMP is a simple, rapid, and cost-effective molecular method with stringent requirements.[27] Positive interpretation in Mtb infection with positive rpoB and specific IS6110, but negative interpretation in NTM infection with positive rpoB and negative IS6110.[28]

**3. Culture Test**

The culture test is the gold standard for the diagnosis and evaluation of NTM infections. There are 2 sample media for Mycobacterium culture, namely (1) Liquid culture media called Mycobacteria Growth Indicator Tubes (MGIT) with a culture time

of 2 weeks, (2) Solid culture media, namely Lowenstein Jensen (LJ) or egg-based medium containing green malachite to inhibit the growth of other contaminating organisms. Even though neither of these tests has a sensitivity of one hundred percent, they are used together.[6,15,29,30]

Rapidly Growing Mycobacteria (RGM) is a new culture medium for major pathogens, including *M. chelonae, M. abscessus* and *M. fortuitum* introduced by Friedmann. RGM media culture is the optimal medium for Rapidly Growing Mycobacteria, while MGIT is optimal for Slowly Growing Mycobacteria and requires a considerable amount of time for pathogen identification.[31,32]

## 4. Histology Test

The examination of tissue samples is not recommended in the diagnosis of NTM if clinical and microbiological criteria already indicate the presence of NTM. Unlike extrapulmonary NTM, tissue samples are recommended for diagnosis of intrapulmonary NTM. Granulomatous inflammation with or without tissue necrosis, and the presence of NTM organisms, is pathognomonic of NTM on histologic examination. However, granulomatous inflammation is not specific to NTM, so histology examination must be complemented by additional diagnostic methods.[21]

At least one culture examination yielded a positive result for NTM growth. On tissue biopsy, neither granulomatous inflammatory tissue nor NTM organisms were detected in immunocompromised patients. In this patient population, histologic characteristics included foamy-histiocytes containing mycobacteria, poor-formed granulomatus, or without inflammatory tissue.[21,22]

## 5. Antimicrobial Sensitivity Test

*Clinical Laboratory Standards Institue* (CLSI) and ATS/IDSA has published criteria for sensitivity testing as the gold standard test for determining microbial susceptibility through culture and microdilution culture growth. In general, NTM sensitivity testing is performed on patients with clinically significant NTM isolates.[21]

In addition, CLSI recommends that CLSI examine NTM species that are infrequently pathogenic, such as *M. gordonae, M. mucogenicum* atau *M. terrae.* The initial screening sensitivity test is the rifampicin sensitivity test. This is followed by other species, such as *M. kansasii*, if rifampicin resistance is detected. In the macrolide group, it is recommended to choose alternative species. MAC are organisms able to lead to macrolide resistance.[21]

So, it can be concluded that the microbiological criteria include:[30]

a. Positive sputum culture from two different sputum samples. If the result is negative, the sputum test and culture must be repeated; or
b. Positive culture of BAL or Bronchial toilet; or
c. *Transbronchial* or Lung biopsy with Mycobacterial histology (Granulomatous Inflammation or AFB) and a positive NTM culture; or

d. Biopsy shows mycobacterial histology (Inflammatory Granulomatus or AFB) and at least one positive sputum or BAL culture for NTM.

## CONCLUSION

Accurate diagnosis of NTM is a challenge for countries endemic to PTB so that pathogen eradication efforts can be well implemented. Mycobacterium infections other than Mtb complex and *M. leprae* were formerly known as MOTT. The switch from MOTT to NTM terminology and the NTM taxonomy can be used as a clinical reference to distinguish between Mtb and NTM infections. Understanding the taxonomy of Mycobacterium is crucial for determining the subsequent diagnostic step. The selection of diagnostic modalities with high sensitivity and specificity is a primary concern for medical professionals. In expediting diagnostics, examination duration and cost-efficiency are also considered.

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Literature Review

# Long COVID-19: Multidisciplinary Approach and Pulmonary Fibrosis Sequelae

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## Abstract

COVID-19 patients may experience a persistent condition of post-COVID-19 infection, which is known as the long-COVID phenomenon or post-acute sequelae of SARS-CoV-2 infection (PASC) or post-acute COVID-19 syndrome (PACS) with long-term sequelae characteristics that stay after the convalescent period of COVID-19 disease. The most common clinical symptoms found within 5 weeks post-infection were fatigue (12.7%), cough (12.4%), headache (11.1%), loss of sense of taste or smell (10.4%), and muscle pain (8.8%). Women have a slightly higher prevalence than men, with a value of 23.6% and 20.7%, respectively, which are dominated by 35-49 years old (26.8%), 50-69 years old (26.1%), and 25-34 years old (24.9%). Pulmonary fibrosis sequelae in COVID-19 occur due to the destruction of the alveolar epithelium and the formation of active myofibroblast foci, causing excessive accumulation of extracellular matrix in lung tissue. Long COVID management requires a multidisciplinary approach, including health workers and the wider community, as well as systematic assessment management. The recommended therapy includes pharmacological (symptomatic, micronutrients, antibiotics, and anti-inflammatory) and non-pharmacological (medical and psychosocial rehabilitation). This review aims to summarize the long COVID and multidisciplinary approach to improve the patient's quality of life.

**Keywords:** COVID-19, fibrosis, long COVID, PACS

## INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a new type of coronavirus that causes respiratory tract infections. This virus was first reported on December 31, 2019 in China. Analysis of isolates from the patient's lower respiratory tract showed the discovery of a new type of coronavirus which was named by the World Health Organization (WHO) as Coronavirus Disease 2019 (COVID-19). SARS-CoV-2 is highly contagious with transmission occurring between species.[1,2] On March 11, 2020, WHO announced that

COVID-19 had become a worldwide pandemic.[3,4]

The number of COVID-19 cases in the world on May 23, 2021, was 165,772,420 confirmed cases and 3,437,545 deaths.[5] Confirmed cases in Indonesia as of May 23, 2021, were as many as 1,736,670 with 47,967 deaths.[6] Until May 23, 2021, 1,414 people had died among the 54,254 confirmed cases in Riau province.[7]

COVID-19 can cause illnesses ranging from asymptomatic, mild, moderate, and severe, to critical symptoms. Common signs and symptoms of COVID-19 infection include fever, cough, sore throat, and shortness of breath, with an average incubation period of 5-6 days and the longest incubation period of 14 days.[8]

Globally, there were 68 million recoveries on January 19, 2021, with or without symptoms, and 2 million deaths from COVID-19. This shows that most people infected with COVID-19 can have no symptoms or recover quickly, but in some cases, clinical symptoms can persist or develop continuously.[2,3]

COVID-19 patients may experience a persistent condition of post COVID-19 infection known as the long-COVID phenomenon or post-acute sequelae of SARS-CoV-2 infection (PASC) or post-acute COVID-19 syndrome (PACS) with long-term sequelae characteristics that persist after the convalescent period of COVID-19.[2,3]

According to WHO, the long COVID syndrome is characterized by the persistence of clinical symptoms in COVID-19 patients, which lasts 4-12 weeks from the initial onset or lasts for 12 weeks or more and is referred to as the chronic post-COVID syndrome.[3] Symptoms of long COVID include fatigue, headaches, shortness of breath, anosmia, muscle weakness, and cognitive dysfunction.[2,3] Carfi et al stated that about 87.4% of COVID-19 patients who have recovered will continue to experience persistent symptoms for up to 60 days.[2,9]

This condition needs to be a concern for health workers because, with prolonged symptoms, the patient's quality of life may decrease, and the clinical deterioration can return to the patient's death.[2,9] The purpose of this literature review is to assess the prevalence, characteristics, clinical manifestations, and management in post-COVID-19 patients with long COVID syndrome and their effect on pulmonary fibrosis formation.

## REVIEW

According to the guidelines of the National Institute for Health and Care Excellence (NICE), the Royal College of General Practitioners (RCGP) and the Scottish Intercollegiate Guidelines Network (SIGN), long COVID is defined as a patient with signs and symptoms that continue or develop after acute infection with COVID-19, including ongoing symptomatic COVID-19 (4-12 weeks) and post-COVID syndrome (12 weeks or more) without other possible causes of illnesses.[10–13]

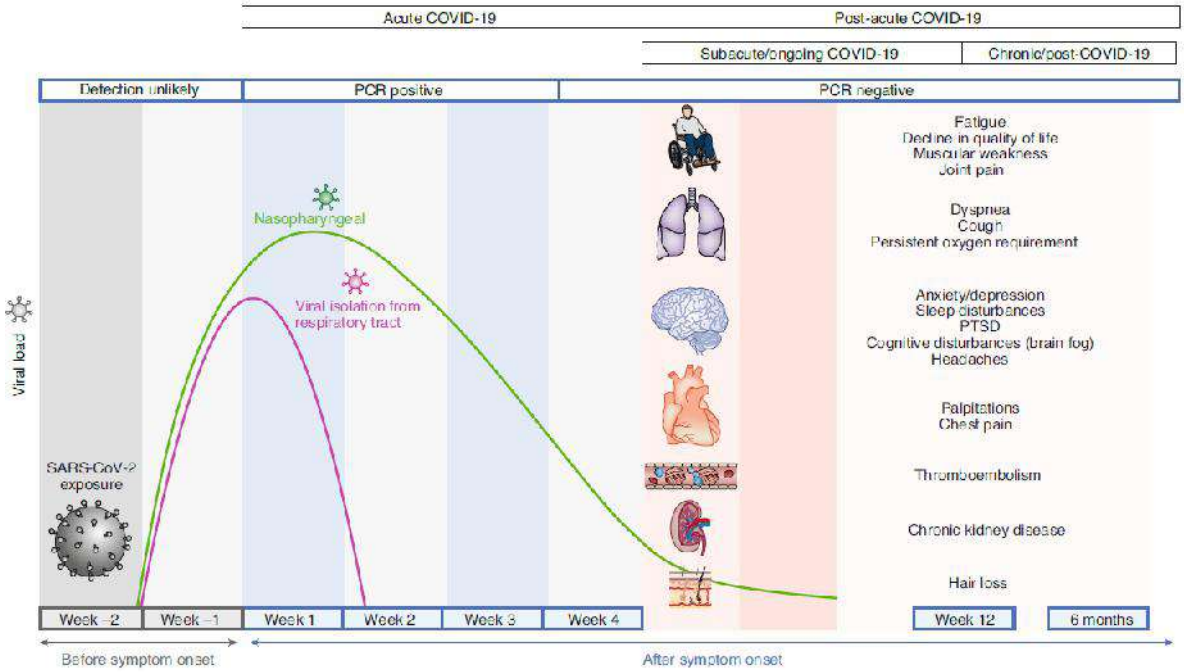


Figure 1. Timeline of COVID-19[14]

*Perhimpunan Dokter Paru Indonesia* (PDPI), or Indonesian Society of Respirology (ISR), in March 2021 issued clinical practice guidelines regarding post-COVID respiratory syndrome. Post-COVID-19 respiratory syndrome, according to PDPI, consists of two categories, namely post-acute COVID-19 syndrome with the onset of persistent pulmonary and respiratory symptoms ≥4 weeks from the onset of COVID-19; and chronic post-COVID-19 with the onset of persistent pulmonary and respiratory symptoms ≥12 weeks from the onset of COVID-19 symptoms.[15]

The definition and timeline of acute post-COVID-19 continue to evolve but are generally defined as persistent symptoms or the development of sequelae more than 3 or 4 weeks after the onset of acute symptoms. Based on the latest literature it is divided into two categories: (1) subacute or ongoing COVID-19 symptoms which include symptoms and abnormalities appearing from 4-12 weeks after acute COVID-19; and (2) chronic or post-COVID-19 syndromes that include symptoms and abnormalities that persist or appear after 12 weeks of the onset of acute COVID-19 and are not attributable to another diagnosis (Figure 1).[14]

Several literatures described multiorgan inflammatory syndrome (MIS) and various organ pathological findings following the incidence of acute infection. Therefore, as standardization of knowledge regarding acute post-COVID-19, it is proposed to divide the clinical manifestations of post-acute COVID-19 into 3 categories, namely: sequelae that persist after recovering from acute infection, organ dysfunction that persists after initial recovery, and new symptoms or syndromes that develop after an initial asymptomatic or mild infection (Figure 2).[16]

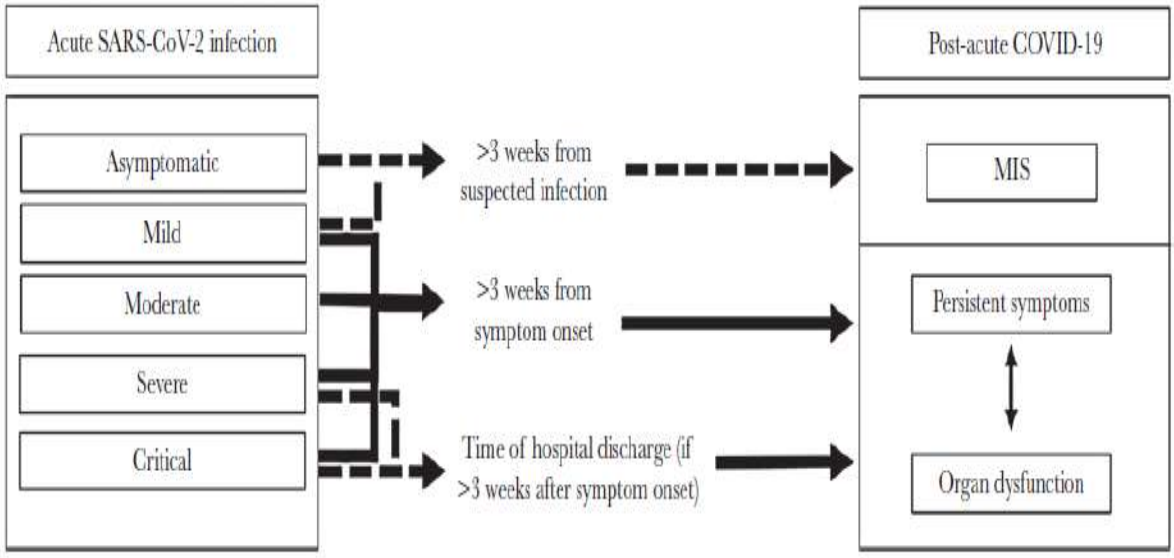


Figure 2. Phase of acute SARS-CoV-2 infection to post-acuteCOVID-19[16]

## Clinical Description

The prevalence of long COVID globally is around 22.1% (95% CI: 21.2% to 23.2%) of patients with a positive test result for COVID-19 who are reported to still have at least 1 symptom within 5 weeks post COVID-19 infection, while 9.8% (7.4% to 13.1%) had symptoms for 12 weeks. The most common clinical symptoms found within 5 weeks post-infection were fatigue (12.7%), cough (12.4%), headache (11.1%), loss of sense of taste or smell (10.4%), and muscle pain (8.8%). Women have a slightly higher prevalence than men, with a value of 23.6% and 20.7%, respectively, which are dominated by the 35-49-year-old (26.8%), 50-69-year-old (26.1%), and 25-34-year-old (24.9%).[17]

## Risk Factor

Epidemiological studies show that long COVID is more common in elderly patients, women, patients with comorbidities, obesity, psychiatric disorders, and those with blood type A. Patients with long COVID tend to experience more acute symptoms. The findings of symptoms such as fatigue, headache, shortness of breath, chest pain when breathing deeply, sensitive skin, hoarseness, and myalgia, as well as clinical findings of signs of the severity of the disease found on CXR during the first hospital visit in the acute phase, are also long-term risk factors for long COVID ($P<0.05$).[10]

In an epidemiological study by Belgian Health Care, the knowledge center reported that there was a statistically significant relationship between comorbidity or underlying medical conditions and clinical symptoms that appeared at the onset of infection with the occurrence of long COVID-19 ($P=0.003$).[10,17] Increased blood urea levels and D-dimer values are also independent biomarkers for the occurrence of pulmonary dysfunction in post-COVID-19 patients within 3 months after

hospitalization. The possible cause of urea and D-dimer being significant biomarkers is not only inflammation but also kidney damage and blood clotting disorders.[11]

## Pathophysiology

Until now, there has not been much literature that clearly explains the pathophysiology of long COVID. In trauma or a severe primary infectious disease such as COVID-19, the systemic inflammatory response syndrome (SIRS) is dominant. This dominant systemic inflammatory response triggers the body's long-lasting compensatory anti-inflammatory response syndrome (CARS). The goal of the CARS response is to reciprocally regulate the systemic inflammatory response to reduce hyperinflammatory conditions, prevent maladaptive multiorgan dysfunction, and restore normal immunological hemostasis.[12]

This anti-inflammatory response syndrome triggers post-infectious or post-traumatic immunosuppression. The simultaneous interaction of several factors plays a role in regulating the balance of pro- and anti-inflammatory responses, namely CARS and SIRS, which determine the impact or outcome of COVID-19. The exaggerated inflammatory response that occurs is the result of (1) exposure to a virus or inoculum, (2) the presence or absence of comorbidities, and (3) an immunocompetent state, and is characterized by excessive release of inflammatory cytokines such as interleukins 1, 6, 8, 17, and 1β, monocyte chemoattractant protein-1, and tissue necrosis factor; collectively known as "cytokine storm".[12]

This process leads to the development of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), coagulopathy, hypotension, hypoperfusion, organ failure (also known as multi-organ failure (MOF) or multi-organ dysfunction syndrome), and death.[12]

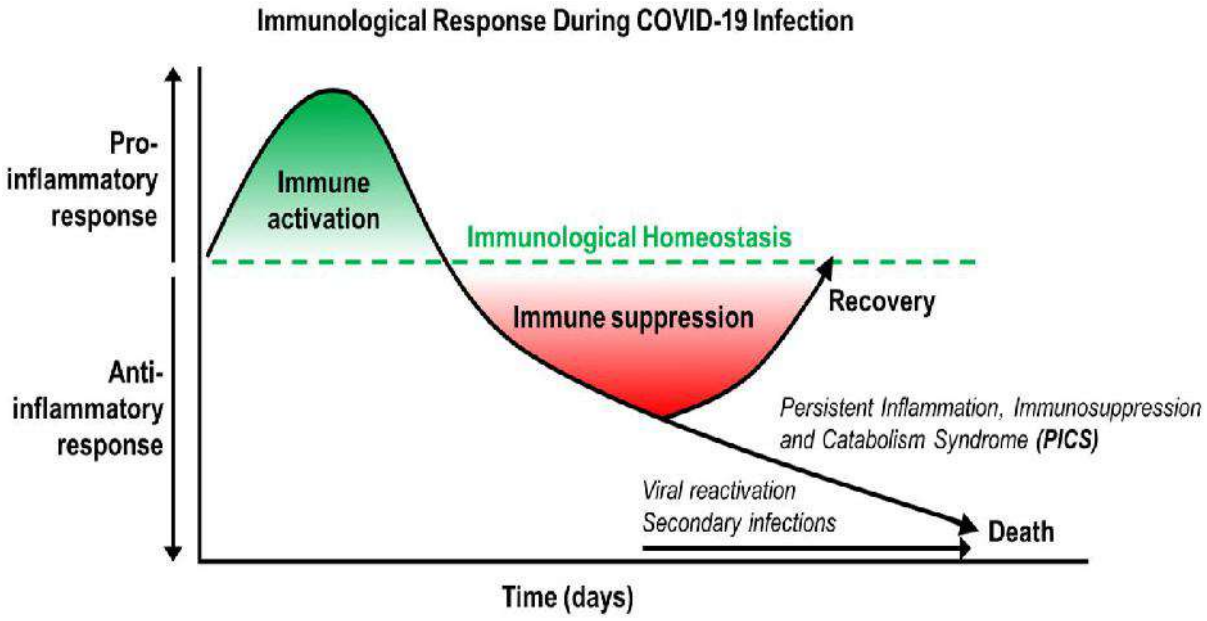


Figure 3. Immunological Respons During Covid-19 Infection[12]

On the other hand, if the inflammatory response is suppressed too far in the direction of CARS, then after the immune system has overcome the initial hyperinflammation caused by cytokine storm and progressed to ARDS, it enters a stage of prolonged immunosuppression, leading to persistent inflammation, immunosuppression, and the catabolism syndrome that becomes one of the hypotheses causing post-acute COVIDsyndrome (PACS) (Figure 3).[12]

Mechanisms regarding post-COVID sequelae include virus-induced cytokine storms and dysregulation of immune responses. Competent viral replication rarely improves within 20 days of symptom onset, suggesting that symptoms are influenced by immunological phenomena. In this immunological phenomenon, the virus persists constantly in the immunological system. This makes it difficult for the virus to be destroyed by the body's immune system and causes endothelial injury and ongoing organ dysfunction, causing acute symptoms after COVID-19 infection.[12]

Mechanisms include a virus-dependent mechanism (invasion of alveolar epithelial and endothelial cells by SARS-CoV-2) and virus-independent mechanism (immunological damage and perivascular inflammation) that damage the endothelial-epithelial barrier by monocyte and neutrophil invasion and extravasation of protein-rich exudate into the alveolar space consistently and cause fibrosis, which is provoked by cytokines such as interleukin-6 (IL-6) and transforming growth factor beta (TGF-β), thus predisposing to bacterial colonization and subsequent infection. The findings in postmortem studies are that the histologic features of lung tissue are accompanied by severe endothelial injury along with the organization and foci of diffuse fibroproliferative alveolar damage, diffuse thrombosis, and microangiopathy.[11,14]

## Impact of Long COVID on the Body

Patients with COVID-19 are dominated by those with mild to moderate symptoms. In total, it is estimated that 10-15% of cases develop severe symptoms, and about 5% become critical. In many patients, some symptoms can persist and occur within weeks to months after recovery. It can also occur in mild cases. In this phase, the patient is no longer infectious.[2] Symptoms after COVID-19 vary between patients. Currently, there are not many clinical studies regarding sequelae after COVID-19.[18]

Several systems or organs of the body can be affected by COVID-19. In the lungs, COVID-19 infection can cause lung tissue damage and pulmonary restriction disorders. Dyspnea, decreased exercise capacity, and hypoxia are the most common persistent symptoms. On investigation, it was found that there was a decrease in the value of the diffusion capacity, ground glass opacity, and fibrosis on radiological examination. Assessment of lung function progression or improvement can be done by checking oxygen saturation, 6-minute walk tests (6MWTs), pulmonary physiology, high-resolution CT

(HRCT) of the chest, and CT angiography if needed.[19,20]

Persistent post-COVID syndrome, also known as long COVID-19, is a pathological entity that includes physical, medical, and cognitive sequelae after COVID-19 infection. Long COVID or post COVID-19 sequelae include persistent immunosuppression and fibrosis in the lungs, heart, and blood vessels. Pathological fibrosis of organs and blood vessels refers to increased mortality and a decreased quality of life. Inhibition of TGF-β, immune modulators, and fibrosis plays a role in this post-COVID sequelae.[12]

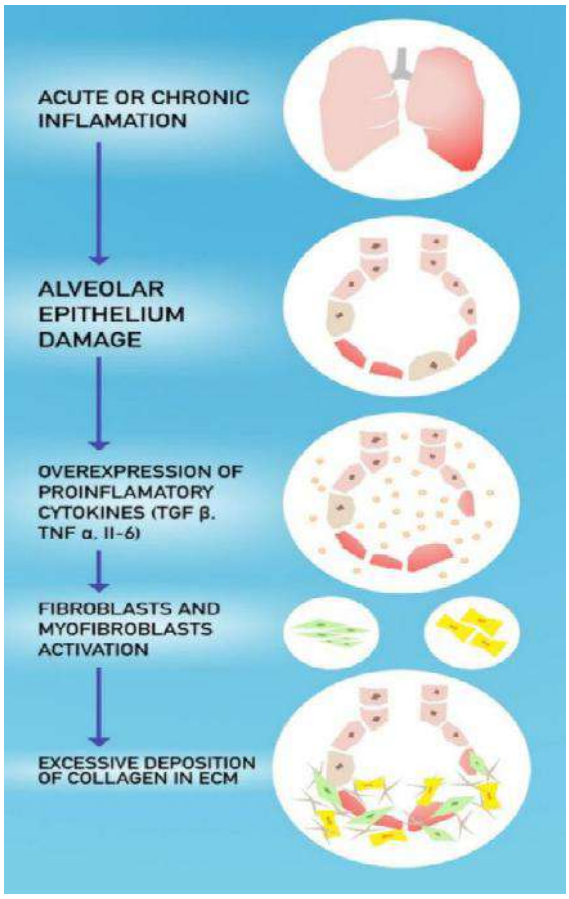


Figure 4. Lung Fibrosis Pathogenesis[19]

Lung tissue analysis of five cases with severe COVID-19-associated pneumonia, including two autopsy specimens and three specimens from the lungs of explored lung transplant recipients, showed histopathology and single-cell ribonucleic acid (RNA) expression patterns similar to those of end-stage pulmonary fibrosis without SARS-CoV infection. This suggests that the majority of individuals infected with COVID-19 develop pulmonary fibrosis, and this occurrence occurs more rapidly in the phase after the resolution of the acute infection.[14]

It has been reported that SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE-2) as a receptor on the human endothelium, causing lung damage and parenchymal lesions. Research on the distribution of ACE-2 in tissues shows that the viral receptor is very broad and expressed in human tissues such as the lungs, digestive tract, kidneys, testes, and other organs. Pulmonary fibrosis is a pathological consequence of acute and chronic interstitial lung disease characterized by damaged alveolar epithelial reconstruction, persistence of fibroblasts, and excessive deposition of collagen and other extracellular matrix (ECM) components with damage to normal lung architecture.[19]

When lung tissue damage occurs, it triggers cells to release excessive growth factors and cytokines, including monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), FGF, PDGF, interleukin-1b (IL-1b), and interleukin-6 (IL-6). Through several studies and scientific literature, serum

levels of these cytokines have greatly increased in COVID-19 patients.[13,19]

This dysregulation of matrix metalloproteinase release causes epithelial and endothelial damage and uncontrolled fibroproliferation. TGF-β regulates fibrosis and, together with VEGF, Il-6, TNF, and vascular dysfunction, participates in the progression to fibrosis due to the differentiation and activation of fibroblasts into active myofibroblast foci that are responsible for the excessive accumulation of extracellular matrix in the basement membrane and interstitial tissue.[13,19]

In the heart, COVID-19 can cause palpitation, dyspnea, chest pain, heart muscle damage, and heart failure. Other sequelae found were myocardial fibrosis, arrhythmias, tachycardia, and autonomic dysfunction due to excessive inflammation of the heart.[21–23] Research conducted by the University of London in 2020 found that of 2739 respondents consisting of post-COVID-19 patients aged >18 years, 86% experienced cardiovascular symptoms, with the percentage of symptoms of palpitations, tachycardia, and chest pain is 68.8%, 61.4%, and 53.1%, respectively.[23]

The impact of COVID-19 on the brain and nervous system is anosmia, venous thromboembolism (pulmonary embolism, heart attack, and stroke), and cognitive disorders such as impaired memory and concentration. In the field of neuropsychiatry, COVID-19 can cause fatigue, myalgia, headaches, anxiety, depression, post-traumatic stress disorder, and sleep disturbances, which are reported to occur in 30-40% of COVID-19 sufferers.[14]

According to data from 2739 respondents in the 2020 of long COVID symptom study by the University of London, which was conducted for 7 months post-acute COVID-19 infection, 72.8% of respondents experienced memory disorders, with short-term and long-term memory disorders of 64.8% and 36.12%, respectively. In addition, other neuropsychiatric impacts were observed, namely 78.6% of respondents experienced sleep disturbances, 57.9% experienced anxiety, 47.3% experienced depression, and 37.6% experienced emotional control difficulties.[23]

This neuropsychiatric disorder is associated with inflammation that occurs in microglia nerve fibers, which causes multisystem disorders ranging from physical to psychological disorders of the nervous system. In the musculoskeletal system, COVID-19 can cause joint and muscle pain and fatigue. This was found in the same study, with a percentage of musculoskeletal disorders as high as 93.9%, with symptoms of chest tightness at 74.8%, followed by myalgia at 69.1%, and joint pain at 52.2%.[23]

## Management

Long COVID management includes a holistic and multidisciplinary approach. Assessment of disease history and symptoms is very helpful in the diagnosis and management of long COVID. Long COVID management requires repeated assessment and evaluation. Management

includes psychological support, supportive investigations, oxygenation therapy if needed, nutritional management, pharmacological therapy, medical rehabilitation, and hospitalization if indicated.[14,15]

The multidisciplinary team in long COVID-19 management includes first-level care in first-rate primary care facilities, pulmonology, cardiology, infectious diseases, neuropsychiatry, pharmacy, occupational health, and health care management, but the involvement of each of these fields varies according to indications.[20] Supportive examinations carried out for long COVID-19 include laboratory tests, oxygen saturation, radiology, lung function, electrocardiography, and quality of life assessment using a questionnaire.[15,21]

Laboratory tests performed include a complete blood count, CRP, ferritin, liver function, kidney function, blood glucose, blood gas and electrolyte analysis, blood coagulation factor, and PCR swab examination. Radiological examination includes CXR and/or thoracic ultrasonography and/or CT scan, and lung perfusion scan if indicated. Lung function tests were also carried out to assess lung physiological disorders.[15,21]

Rintatolimod is the first successful immunomodulatory drug for the treatment of phase II/III encephalomyelitis/chronic fatigue syndrome (ME/CFS). This therapy has the potential to improve the symptoms as well as therapy in long COVID-19 so that it can improve the patient's quality of life. Another therapy recommended for long COVID is an agonist against mast cell activation syndrome (MCAS).[11]

Mast cell activation syndrome causes multisystem inflammatory and allergic disorders, and triggers the activation of fibroblast factors that could lead to pulmonary fibrosis, which is often found in COVID-19 patients. The SARS-CoV2 virus has been reported to trigger mast cell responses along with other immune cells, given that MCAS and COVID have a similar underlying mechanism and range of therapeutic choices. Managing mast cell-mediated hyperinflammation states and reducing symptoms further may be advantageous for patients' long-term control and recovery.[11]

Other pharmacological treatment options include antiallergic antihistamines (olopatadine and ketotifen), anti-inflammatory antibiotics (clarithromycin), and corticosteroids (hydrocortisone and dexamethasone). The persistence of SARS-CoV-2 is one factor that contributes to the occurrence of long COVID. A pilot clinical trial project on long COVID therapy in 2020 in India reported that vitamin D3 therapy in the oral form of cholecalciferol could increase viral clearance, which shortened the duration of SARS-CoV-2 infection.[11]

Oral cholecalciferol also decreased fibrinogen levels in infected individuals, thereby improving pulmonary fibrosis. Following the results of this study, antifibrotic therapy (nintedanib and pirfenidone) became the recommended potent therapeutic option to treat the long-term effects of pulmonary fibrosis in COVID-19. Another therapeutic option is

probiotics. Probiotics and prebiotics have been recommended as supplements in COVID-19 patients, referring to their safety and benefits as systemic immunomodulators in the regulation of the lung-digestive tract axis.[11]

Non-pharmacological therapy in the field of pulmonology includes pulmonary rehabilitation, oxygen therapy, psychotherapy, adequate nutrition, and hospitalization, as indicated.[15] Functional rehabilitation is one of the recommendations that has proven to be meaningful in the management of long COVID. In rehabilitation, patients are encouraged to perform light aerobic movements that depend on each individual's capacity.[2,11]

The difficulty level of rehabilitation is increased according to the level of tolerance until clinical improvement is seen (4-6 weeks). The rehabilitation carried out includes breathing exercises to increase the efficiency of the respiratory muscles and diaphragm. This exercise is done for 5-10 minutes per day. This rehabilitation exercise is good for patients with chronic obstructive pulmonary disease, acute respiratory depression syndrome, and COVID-19. These medically modifiable and supportive capabilities can help maintain quality of life and mental health.[2,11]

## CONCLUSION

Pulmonary fibrosis in COVID-19 occurs due to the destruction of the alveolar epithelium and the formation of foci of active myofibroblasts, causing excessive accumulation of extracellular matrix in lung tissue. Long COVID management requires a multidisciplinary approach, including health workers and the wider community, as well as systematic assessment management. Referrals to specialists are recommended as indicated. The recommended therapy includes pharmacological (symptomatic, micronutrients, antibiotics, and anti-inflammatory) and non-pharmacological (medical and psychosocial rehabilitation).

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Literature Review

# Oxygen Therapy in Exacerbation of Interstitial Lung Disease

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## Abstract

Interstitial lung diseases (ILD) are a group of diseases that involve damage in the interstitial tissue, causing diffusion disorders which ultimately lead to hypoxemia. One of the conditions that aggravate hypoxemia in ILD patients is acute exacerbation. Acute exacerbation is a condition of deterioration of ILD that can occur in less than 1 month. During an acute exacerbation, there will be a worsening of the HRCT pattern with increased ground glass opacities and a worsening of the clinical picture including hypoxemia. Acute exacerbations are closely related to increased mortality rates. Oxygen administration is one of the supportive therapies that can be given to acute exacerbations. The provision of oxygen therapy is adjusted to the patient's needs using a high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation.

**Keywords:** acute exacerbation, interstitial lung disease, oxygen therapy

## INTRODUCTION

Interstitial lung disease (ILD) comprises a diverse spectrum of conditions by the presence of extensive fibrous abnormalities with varying degrees of hypoxemia. The most frequent symptoms are cough and dyspnea.[1] Lung parenchymal tissue damage is indicated by inflammation, fibrosis, typical clinical presentation, and radiological manifestation. Oxygen therapy is commonly given to ILD patients to reduce shortness of breath and increase physical capacity through better gas exchange. Although frequently used, there is only little evidence supporting its effectiveness in treating ILD.[1,2]

The American Thoracic Society (ATS) defines acute exacerbations of interstitial lung disease (AE-ILD) as clinically acute respiratory deterioration that evolves in less than one month without any other etiology. Initially, the term AE-ILD in IPF commonly appears as acute lung injury (ALI) pathologically and diffuse alveolar damage (DAD) histopathologically in most cases.[3] This review will discuss the role of

oxygen therapy in treating patients with ILD.

## INTERSTITIAL LUNG DISEASE

Interstitial lung disease refers to an extensive range of conditions characterized by lung fibrosis, classified according to physiological, pathological, radiographical, and clinical factors. Measuring the incidence of ILD in the United States poses a significant challenge because it is part of the exclusion diagnosis requiring extensive investigation. However, current guidelines and classification further ease the diagnostic process of ILD. Approximately 30 cases per 100,000 are reported each year, resulting in an overall prevalence of 80.9 and 67.2 per 100,000 population per year in men and women. The ILD classification system categorizes the diseases using clinical, histopathological, and radiological parameters.[2]

Classification of ILD groups according to etiologies could help differentiate endogenic and exogenic factors.[2] Others are classified according to the clinical, histopathological, and radiological parameters. Some known causes include occupational and environmental exposure, autoimmune disease, and idiopathic diseases. Idiopathic lung fibrosis had the worst prognosis, with an overall survival of only two to three years since the diagnosis.[2,4]

Meanwhile, connective tissue disease-associated interstitial lung disease (CTD-ILD) had a better prognosis, with an overall survival of 6.5 years. Among other ILDs, sarcoidosis has the best prognosis with a 5-year overall survival rate of 91.6%, compared to that of CTD-ILD and IPF, which are 69.7% and 35%, respectively.[2]

## EXACERBATION OF INTERSTITIAL LUNG DISEASE

### Definition

The ATS defines acute exacerbations of interstitial lung disease (AE-ILD) as clinically acute respiratory deterioration that evolves in less than one month without any other etiology. On the other hand, the clinical trials network defines interstitial pulmonary fibrosis (IPF) exacerbation as a worsening in pulmonary function that occurs in less than one month, followed by radiographical abnormalities on HRCT examinations such as an increase of ground-glass opacification features without other definitive causes such as fluid overload, heart failure or pulmonary embolism.[3] AE-ILD often leads to poor prognosis and high mortality.[5]

Symptoms like productive or dry cough, an increase of sputum production and fever were related to the rapid worsening of the respiratory symptoms in less than one month. Many patients often require admission to the intensive care unit where ventilatory support is urgently needed due to severe hypoxemia in arterial blood gas and respiratory failure.[3,6–8]

Abnormal gas exchange criteria are the condition of $PaO_2/FiO_2$ ratio <225 or a decrease in $PaO_2$ ≥10 mmHg. Until now, AE-ILD diagnosis has relied on clinical and

radiological findings. Bronchoscopy with bronchoalveolar lavage (BAL) in IPF patients is considered to rule out the cause of infection. However, a study showed a similar outcome irrespective of whether the cause of the exacerbation could be identified or not, as seen in idiopathic cases.[5]

## Epidemiology

Understanding the epidemiology of AE-ILD precisely is challenging due to the lack of clear understanding regarding its diagnostic criteria, patient population, the severity of the underlying disease, follow-up period, and statistical methodology. Retrospective cohort studies typically report a higher incidence and prevalence of AE-ILD. However, they may be biased towards reporting acute deterioration from known causes, such as pulmonary embolism and heart failure, as acute exacerbation of pulmonary interstitial fibrosis. A meta-analysis of seven prospective multicenter trials described an overall incidence rate of 26.3 per 1,000 patient-year (ranging from 8.9 to 206.3 per 1,000 patients). Prospective clinical trials often exclude patients with advanced disease and comorbidities. Additionally, as the risk of acute exacerbation (AE) increases with ILD severity, the incidence of AE may be higher than that estimated by the prospective studies.[9]

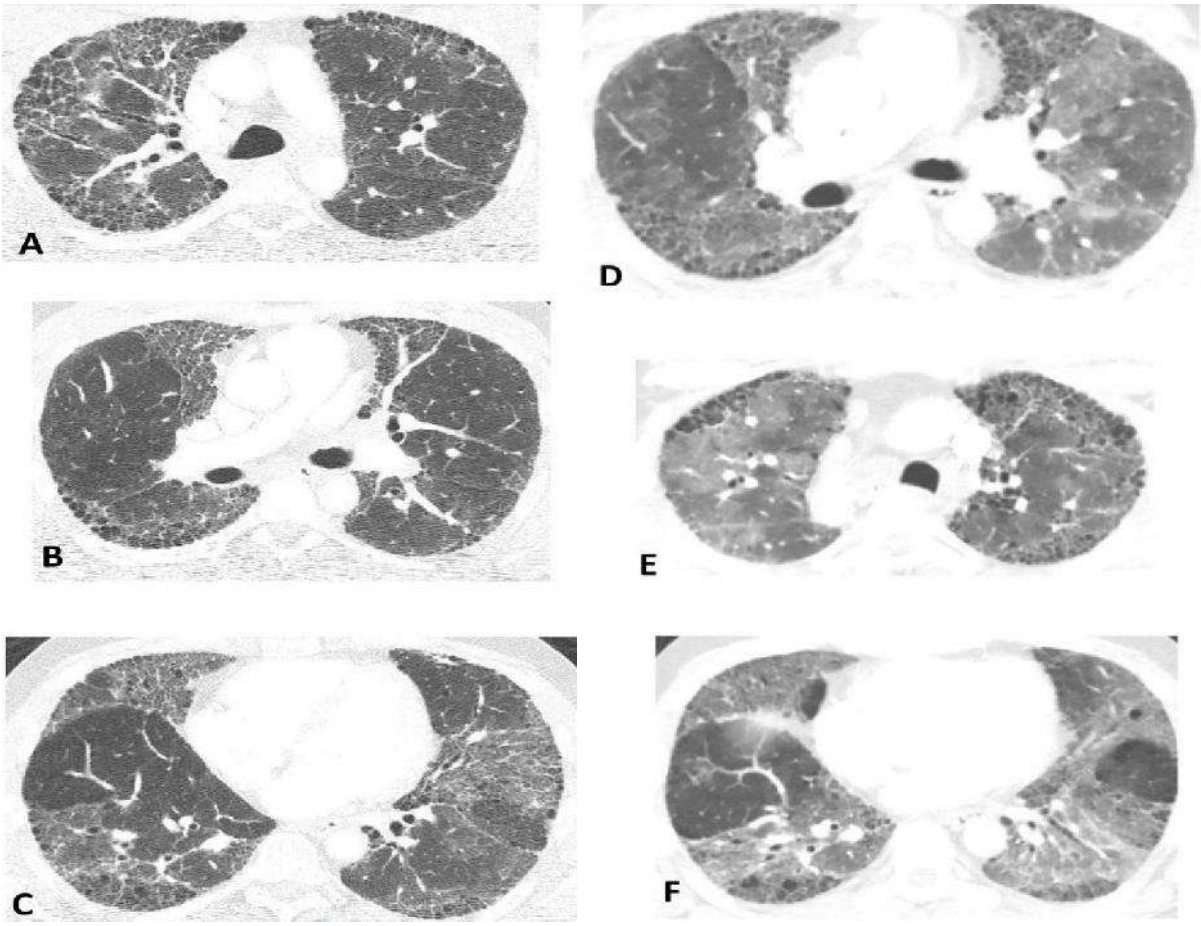


Figure 1. HRCT of a 50-year-old patient's upper, middle, and lower lung lobes (A, B, C) and HRCT images of the same patient taken 2 months later (D, E, F) showing a worsening of shortness of breath[8]

## Etiology

The etiology of AE-ILD, encompassing its onset and progression remains unpredictable. Currently, it remains unclear whether AE-ILD is initiated by intrinsic factors driving the disease's progression, manifesting as a response to external factors (such as infection, microaspiration, pulmonary embolism, mechanical stress), or both.[6,9] AE-ILD had a poor prognosis and high mortality within 6 to 12 months.[3] Nevertheless, further research is needed to pinpoint the main causes of AE-ILD and any potential biomarkers.

## DIAGNOSTIC CRITERIA OF ILD EXACERBATION

Four diagnostic criteria for IPF exacerbation include a previous or concurrent diagnosis of IPF at the time of exacerbation, acute worsening of dyspnea in less than 1 month, opacity or ground-glass consolidation in both lungs, with a background pattern consistent with usual interstitial pneumonia (UIP) on a computed tomography (CT) scan, and lung damage that cannot be explained as heart failure or fluid overload. Certain conditions need to be ruled out as a preliminary when considering the diagnosis of AE-IPF, such as pneumothorax, cardiogenic lung edema, lung embolism, ALI, or ARDS with an identifiable cause, lower respiratory tract infection, and pulmonary hypertension.[10]

Faverio et al elaborate that Acute Respiratory Failure (ARF) in known chronic ILD should be followed with laboratory examination, CT scan (CT angiography if pulmonary embolism is suspected), and bronchoscopy to determine a work-up diagnosis. If contributing factors are not identified, AE-ILD could likely be the cause of ARF and other differential diagnoses (e.g. pulmonary embolism, congestive heart failure, infection, pneumothorax, drug-induced lung toxicity, diffuse alveolar hemorrhage) can be excluded. The worsening of AE-ILD can be triggered by occult infection, micro-aspiration, post-procedural or happens idiopathically.[11]

## EXACERBATION MANAGEMENT

The AE-ILD management approach includes oxygenation, corticosteroids, antifibrotic, pulmonary hypertension treatment, and intensive and palliative care.[12] Until now, no study has conclusively determined the most optimal management for AE-ILD.[5,8] However, it is imperative that ILD patients utilize oxygen therapy as it has been proven to relieve shortness of breath.[13]

The international guideline for IPF management recommends supportive treatment to relieve symptoms and long-term oxygen therapy. In addition, patients are also prescribed corticosteroids as few studies have shown their benefit in patients with idiopathic AE-ILD, CTD-ILD, sarcoidosis, and certain hypersensitive pneumonitis.[5]

Methylprednisolone administered at a daily dose of 500-1000 mg for three days, followed by a daily dose of 1 mg/kg of body weight, is a frequently reported treatment

despite its unclear effect.[8] Monitoring for steroid-related kidney side effects is crucial, particularly in patients with systemic sclerosis-associated ILD (SSc-ILD). Identifying and eliminating toxic exposure should be done among AE-ILD patients receiving broad-spectrum antibiotics.[5]

Empiric antibiotic treatment is recommended until infection can be ruled out. Research has indicated that procalcitonin levels can guide the duration of antibiotic treatments, thus preventing prolonged and unnecessary use. However, no significant difference in outcome was reported compared to the control group.[8]

Mechanical ventilatory support can be provided to ILD patients with hypoxic respiratory failure. However, a case-by-case assessment is highly encouraged because its use is associated with a higher mortality rate. A few small studies suggest using only nasal cannula oxygen as a supportive measure thereby avoiding the need for intubation or mechanical ventilation. Nonetheless, some conditions warrant invasive ventilatory support, such as with deteriorating IPF patients where lung transplantation is considered.[5]

Extracorporeal membrane oxygenation (ECMO) can be employed in patients experiencing an acute exacerbation of IPF, potentially reducing the risk of developing chronic conditions. Additionally, this management method can be applied to patients with fatal lung conditions such as ARDS and cardiogenic shock, or those awaiting lung transplants.[5] The extracorporeal system provides pulmonary support through venovenous (VV) settings or both circulatory and breathing support through the veno-arterial (VA) configuration.[5,14]

## OXYGEN THERAPY

The prevalence of hypoxemia among ILD patients remains unclear due to the lack of standardization in its definition and the required diagnostic modality to specify the type of hypoxemia: resting, activity-related, or nocturnal. Resting hypoxemia is characterized by advanced-stage chronic lung disease and defined by resting oxygen pressure ($P_aO_2$) of ≤55 mmHg or 56-59 mmHg with evidence of organ damage (cor pulmonale, polycythemia, and/or pulmonary hypertension). Meanwhile, exertional or activity-related hypoxemia is defined by the lowest peripheral oxygen saturation of ≤88% and A decrease of ≥4% with or without the lowest $SpO_2$ of <90%.[6,15]

Exertional hypoxemia occurs more commonly in interstitial lung disease. Another type of hypoxemia is nocturnal hypoxemia, which affects 36-57% of ILD patients. It is defined as a breathing disorder during sleeping that is not necessarily correlated with lung function impairment's degree. A study discovered a potential relationship between nocturnal hypoxemia and pulmonary hypertension among patients with chronic obstructive pulmonary disease (COPD) and ILD.[6]

A systematic review also identified that ILD patients were at risk for nocturnal hypoxemia due to ventilation restriction

and dysregulated gas exchange, which worsens when they sleep in a supine position and experience a decrease in ventilatory drive during sleeping.[16]

The primary mechanism of pulmonary artery hypoxemia in ILD patients is an imbalance in the ventilation-perfusion ratio (V/Q), progressive destruction of the alveolar unit, and limited oxygen diffusion from the alveoli into the capillaries. Patients with ILD also exhibit a significant increase in respiratory rate during physical activity, with reduced tidal volume (Vt) and an increase in dead space and tidal volume ratio (RV/Vt). These factors clarify the mechanism behind the physical activities leading to the decrease in $PaO_2$, which is one of the main factors correlated with a worse prognosis.[7]

## High-Flow Nasal Cannula

Acute exacerbation stands as the primary fatality contributor among ILD patients with lung fibrosis, frequently accompanied by severe hypoxemia. Patients with invasive mechanical ventilatory support have a poor prognosis. Limited studies with small participants showed that non-invasive positive pressure ventilation (NPPV), utilized to mitigate the complication of endotracheal intubation, can improve the prognosis of patients with lung fibrotic disease. Nonetheless, there is a lack of comprehensive knowledge regarding its efficacy and tolerability in the management of AE-ILD.[17]

The high-flow nasal cannula (HFNC) recently was considered a new oxygen-delivering device that has the advantage of delivering heated and moisturized inspired gas with a high flow (up to 60 liters/minute), allowing an increase in inspired oxygen fraction ($FiO_2$) to 1.0 (100%).[17,18]

A randomized controlled trial showed HFNC was found equally effective as NPPV in managing acute respiratory failure arising from diseases such as pneumonia and pulmonary edema. The high-flow nasal cannula is reported to be more suitable in treating acute respiratory failure caused by an acute exacerbation of interstitial pneumonia (AE-IP) compared to lung edema or acute exacerbation of COPD, which may need higher positive end-expiratory pressure and/or ventilatory support.[17,18]

There are three case reports from Japan in 2016 on the use of HFNC in AE-IP patients. These case reports found two clinically significant discoveries; HFNC could rapidly increase oxygenation in AE-IP patients with respiratory failure that cannot be adequately managed with standard oxygenation therapies. High-flow nasal cannula can immediately correct severe hypoxemia caused by AE-IP with a $PaO_2/FiO_2$ ratio of <0.2. Those case reports did not provide guidelines for the initial protocol when using HFNC in AE-IP patients.[19,20]

However, a $FiO_2$ between 0.7-1.0 and a flow rate of 40 liters/minute was shown to be successful in increasing $PaO_2$. Additionally, HFNC can promptly decrease patients' respiratory rate and relieve dyspnea, even in those with chronic respiratory failure or widespread lung

opacities. HFNC was also reported to have a similar effect in acute respiratory failure caused by other etiologies, such as pneumonia.[19,20]

High-flow nasal cannula offers several benefits compared to other standard oxygen therapies by regularly flushing out the upper airway space to reduce lung dead space. Furthermore, positive air pressure as low as 3-7 $cmH_2O$ can be adjusted automatically, resulting in high compatibility between ventilation and perfusion and thus reducing the overall work of breathing.[17,18] The use of HFNC both in acute respiratory failure patients or stable IPF, has been proven to enhance ventilation efficiency, decrease work of breathing, and lower respiratory rate and minute volume, all without causing an elevation in capillary $PCO_2$ levels.[19,20]

Another significant finding is that AE-IP patients tolerated HFNC well over three weeks. In a case report from Japan, the patient was safely transitioned between days 21 and 26 from HFNC. In line with this finding, Boyer et al reported a case of AE-IPF patients treated with HFNC in combination with a high-dose corticosteroid and cyclophosphamide for five weeks.[21]

Conversely, other studies showed that the mean of NPPV duration use for AE-IP patients was 11.7 days.[22,23] Several studies have shown that the use of HFNC provides greater comfort compared to the use of NPPV. Due to its efficacy and the minimal discomfort, the transition from HFNC to a standard oxygenation system could be postponed until the $FiO_2$ reaches a value of 0.35-0.4 at a flow of 35-40 liters/minute.[24]

## Non-invasive ventilation

Non-invasive ventilation is initiated in every patient showing $CO_2$ retention ($PaCO_2$ ≥45 mmHg) and signs of respiratory muscle fatigue (dyspnea, tachypnea, or abdominal paradox) after experiencing hypoxemia with conventional oxygen therapy of HFNC. Non-invasive ventilation is delivered through a portable ventilator set on pressure support (PS) ventilation mode. Initially, pressure support is adjusted to achieve a moderate tidal volume (6-8 ml/kg of body weight), and the ventilator settings are then adjusted based on blood gas analysis (BGA) data to ensure adequate gas exchange. Though not always optimal, this approach aims to protect the lungs from the risk of ventilator-induced lung injury (VILI).[25]

The PS level should not exceed 25 $cmH_2O$. The end expiration positive pressure is typically set at 5 $cmH_2O$ and is incrementally increased by approximately 1-2 $cmH_2O$, not exceeding 6-8 $cmH_2O$ due to the higher risk of pneumothorax. Additional oxygen is introduced into the ventilator circuit, with the oxygen flow rate adjusted to achieve an arterial $SaO_2$ of >92% or $PaO_2$ >65 mmHg. The NIV device used allows for the utilization of a full-face mask.[24]

A study observing the use of NIV in ILD patients found that 28 patients (47%) and 26 patients (44%) presented with UIP and NSIP radiological patterns, while 6 patients (9%) manifested varied

radiological patterns such as consolidation and ground-glass appearance.[26]

### Invasive mechanical ventilation

Patients who are not on the list for transplant candidates usually have a poor prognosis after ICU admission. Many patients experiencing acute respiratory failure due to ILD will receive little to no benefit from prolonged intensive care. As explained above, HFNC and NIV are potential alternatives to endotracheal intubations in ARF cases. The management algorithm does not consider elective intubation and intermittent mandatory ventilation (IMV) after NIV failure. Emergent intubation is performed under the following conditions: respiratory arrest, loss of consciousness with a respiratory pause, gasping, heart rate of <50 times/minute with loss of awareness, and hemodynamic instability with a systolic blood pressure of <70 mmHg.[24,25]

### Extracorporeal Membrane Oxygenation

The management of ILD and acute respiratory failure patients presents its own set of challenges. Currently, lung transplantation is the definitive therapy for refractory ILD, and it applies only to stable patients who are already on the transplantation list. Extracorporeal membrane oxygenation (ECMO) is considered for ILD patients with severe respiratory failure or ongoing refractory hypoxemia, uncompensated hypercapnia, or acidemia despite maximal medical therapy and using HFNC or ventilatory support.[23] The use of ECMO will be determined when at least two intensivists agree on the potentially reversible cause of the deterioration (for example, infection or lung embolism) and if the patients provide consent, whether they are previously candidates or non-candidates for transplantation. ECMO is denied in patients with underlying advanced disease or poor prognosis, where comorbid conditions may impede the treatment.[14,27,28]

ECMO usage on ILD with severe respiratory failure can be more beneficial than IMV. Complications such as ventilator-associated pneumonia (VAP) and ventilator-induced lung injury (VILI) can be prevented. Oral feeding, spontaneous coughing, and social interaction can be preserved. Moreover, early rehabilitation can be initiated.[11]

Fuehner et al compare the outcome of awake-ECMO patients with terminal respiratory candidates to lung transplant to a historical cohort of patients with IMV as a bridge to transplant. The result shows an 80% 6-month survival rate after transplantation in an awake-ECMO group, whereas a 50% survival rate in the IMV group. ECMO minimizes the risk of fatal deterioration of underlying chronic processes that are most likely triggered by IMV invasiveness. However, ECMO does not change the poor outcome of severe ARF in ILD. The usage should be limited to patients with good short-term prognosis.[29]

## PROGNOSIS

AE-ILD is a life-threatening event with a high mortality rate. Among 35-46%

of IPF deaths are caused by AE-IPF. The median survival after AE-IPF ranging 1 to 4 months. Some potential prognostic factors include lower FVC and DLCO, higher fibrosis score, extensive findings in HRCT, and several markers such as lactate dehydrogenase (LDH), C-reactive protein (CRP), KL-6, circulating fibrocytes, and anti-HSP70 autoantibodies.[3]

Oxygen therapy can be associated with epithelial damage that may lead to lung injury. Reports in acute clinical settings show increased mortality with high targets of oxygen saturation or high-flow oxygen supplementation. It is postulated due to the accumulation of reactive oxygen species (ROS). Studies assessing this theory are still on further research. Oral administration of N-acetyl-cysteine, an antioxidant, shown to suppress systematic oxidative stress levels induced by oxygen therapy in COPD patients. Pirfenidone, an antifibrotic agent for ILD treatment, has shown antioxidant effects in experimental models. However, the therapeutic effects of antioxidative properties in ILD patients with oxygen therapy are yet to be evaluated.[30]

## CONCLUSION

AE-ILD diagnosis should be based on clinical presentation, physical examination, and additional tests. The approach to AE-ILD management includes oxygenation, corticosteroids, antifibrotic, pulmonary hypertension treatment, also intensive and palliative care. Administering supportive oxygen therapy could potentially improve patients' clinical outcomes. Randomized control studies have shown that HFNC has the same efficacy as NPPV in managing acute respiratory failure attributed to alveolar lung diseases such as pneumonia and lung edema.

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Literature Review

# Rehabilitation Management for Sarcopenia in Chronic Obstructive Pulmonary Disease: A Literature Review

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## Abstract

Chronic obstructive pulmonary disease (COPD) is a prevalent and debilitating chronic respiratory condition that not only affects the lungs but has far-reaching systemic consequences; one such consequence is the heightened risk of developing sarcopenia, a condition characterized by progressive loss of skeletal muscle mass and strength. Recent studies have highlighted the significant prevalence of sarcopenia among COPD patients, with rates ranging from 7.9% to 66.7%. This association underscores the importance of early identification and intervention to mitigate the adverse outcomes related to both conditions. Managing COPD patients with sarcopenia is fraught with challenges, primarily due to the multifaceted nature of both conditions. Sarcopenia exacerbates the decline in respiratory function and physical performance in COPD patients, complicating treatment and management strategies. The complexity is further amplified by the need for personalized treatment plans that address these conditions' pulmonary and musculoskeletal aspects. Precise assessment and re-evaluation are essential to ensure optimal outcomes and enhance physical and functional well-being. Rehabilitation for COPD patients with sarcopenia involves a multidisciplinary approach, focusing on exercise training, nutritional support, and pulmonary interventions. Pulmonary rehabilitation programs, tailored to individual patient needs and capabilities, have shown promise in improving exercise capacity, functional performance, and overall health status, thereby enhancing the quality of life for these patients. In this literature review, we will discuss the elevated risk of sarcopenia in COPD patients, highlight the significance of rehabilitation management, and emphasize the pivotal role of precise assessment and re-evaluation in optimizing the care provided to this population.

**Keywords:** COPD, exercise, rehabilitation, sarcopenia

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a primary global health concern and is one of the leading causes of death worldwide, particularly in developing countries. Although a preventable disease, COPD is the third leading cause of death globally, with 90% of mortality occurring in developing countries. The most common cause of COPD development in middle age is chronic smoking.[1,2]

COPD is characterized by persistent airflow limitation primarily due to inflammation of the respiratory tract and lungs caused by exposure to harmful gases or particles. Critical symptoms of COPD include chronic respiratory distress, such as dyspnea, chronic cough, sputum production, and exacerbations.[1,2]

Chronic obstructive pulmonary disease not only affects the respiratory system but also has systemic implications, often coexisting with other medical conditions, such as cardiovascular disease, metabolic syndrome, osteoporosis, depression, and anxiety. Moreover, COPD leads to skeletal muscle dysfunction, resulting in sarcopenia and cellular abnormalities. Sarcopenia is characterized by decreased muscle mass and/or impaired muscle function, often accompanied by symptoms such as fatigue and reduced physical activity.[3]

Sarcopenia occurs at a notably high rate among individuals with COPD. The prevalence of sarcopenia in patients with COPD varies significantly across different studies, primarily due to differences in the populations studied, the methods used to assess sarcopenia, and the definitions of sarcopenia used. A systematic review and meta-analysis found that the prevalence of sarcopenia in COPD patients ranged from 7.9% to 66.7%, with an overall prevalence of 21.6%.[3]

The occurrence of sarcopenia linked to COPD is affected by various risk factors, which include the severity of lung disease and other clinical conditions, such as systemic inflammation, oxidative stress, smoking, low oxygen levels, reduced physical activity over time, and malnutrition.[3]

The interaction between sarcopenia severity and respiratory dysfunction may be critical for the prognosis or progression of COPD. This Literature Review aims to provide insights into the current knowledge regarding Sarcopenia in COPD. Based on the recent research findings, it explores the pathogenesis mechanisms, contributing factors, clinical implications, assessment methods, and management strategies for COPD patients, focusing on rehabilitation.

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease that can be prevented and treated. It causes persistent airflow limitation that usually worsens over time, excessive chronic inflammation of the airways and lung parenchyma due to exposure to harmful gases or particles, and chronic respiratory distress such as shortness of breath,

coughing, sputum production, and flare-ups.[1,2]

Significant systemic consequences are associated with COPD, indicating the existence of underlying concomitant diseases. The impact of COPD on each individual varies according to the severity of symptoms, primarily dyspnea and decreased exercise capacity, systemic implications, and other concurrent conditions.[1]

Several factors contribute to COPD pathological changes: structural changes such as an increase in goblet cells and enlargement of submucosal glands contribute to excessive mucus production, metaplasia of squamous epithelial cells, alveolar wall degradation and death of epithelial and endothelial cells, manifest as emphysema.[2]

In addition, structural abnormalities in pulmonary blood arteries, such as intimal thickening, endothelial cell dysfunction, and smooth muscle hypertrophy, contribute to pulmonary hypertension.[2,4] Diaphragm dysfunction in individuals with COPD is a consequence of dynamic hyperinflammation, leading to mechanical losses and weakness. During exacerbations, this weakness is driven by increased numbers of lung inflammatory cells, oxidative stress-induced diaphragmatic damage, ongoing diaphragm remodeling processes, the persistence of hyperinflammatory areas that disrupt diaphragmatic performance, and dynamic changes in mitochondrial function.[4]

## COPD Implications

The COPD exacerbation and episode of hospitalization have various non-pulmonary consequences due to medical approaches. Systemic inflammation, high doses or prolonged use of corticosteroids, oxidative stress, hypoxia, and hypercapnia could cause further cardiac disease, impaired glucose control, and other complications.[5]

During hospitalization, patients' immobility, imbalance of catabolic-anabolic metabolism, and reduced dietary intake may lead to sarcopenia, malnutrition, rapid deconditioning, osteoporosis, cognitive impairment, and, at last, self-efficacy and the patient's confidence. The above has a more significant impact, such as increased readmission, disability, and even death.[5]

Multimorbidity in patients with COPD is frequently associated with cardiovascular disease, metabolic syndrome, osteoporosis, depression, and anxiety. Additionally, COPD exerts a significant impact on extrapulmonary manifestations, referred to as systemic effects of COPD. These systemic effects encompass weight loss, nutritional abnormalities, and skeletal muscle dysfunction.[1,4]

In COPD, there is a 2-3 times higher risk of cardiovascular disease; even mild COPD contributes significantly to the pathobiology of cardiovascular abnormalities.[6] Skeletal muscle dysfunction is characterized by sarcopenia and cellular function abnormalities. The underlying mechanisms of systemic effects need further investigation, as they are multifactorial, involving factors such as

inactivity, an unhealthy diet, inflammation, and hypoxia. These factors contribute to exercise intolerance and suboptimal health status in COPD patients. Therefore, addressing systemic effects is crucial to reduce morbidity in COPD patients, and it should be assessed and managed based on individual patient conditions.[1,6]

Nutritional abnormalities are common among individuals with COPD, and these abnormalities involve various aspects of their dietary and metabolic profiles. This includes changes in caloric intake, basal metabolic rate (BMR), intermediary metabolism, and body composition. Unexplained weight loss is a noteworthy aspect of COPD-related nutritional abnormalities. Up to 50 percent of persons with severe COPD and persistent respiratory failure are susceptible to this phenomenon. Surprisingly, about 10 to 15 percent of people with mild to moderate COPD also have this condition. Loss of skeletal muscle mass, accompanied by a fall in fat mass, is a significant cause of weight loss in COPD patients.[6]

Exception of patients experiencing disease exacerbations: these nutritional abnormalities are not typically related to a lower caloric intake. Instead, COPD patients generally have a greater basal metabolic rate (BMR), which might contribute to weight loss. This higher BMR can be caused by many causes, including elevated respiratory effort, the use of commonly prescribed COPD medications (such as 2-agonists), systemic inflammation, and tissue hypoxia.[6]

In conclusion, nutritional abnormalities and unexplained weight loss are essential concerns in COPD patients, as they arise from complicated interactions involving metabolic and inflammatory variables, as opposed to calorie restriction alone. Understanding these mechanisms is necessary to develop practical solutions to treat dietary difficulties and weight loss in COPD patients.[6]

Skeletal muscle dysfunction in patients with COPD is characterized by specific anatomical changes, such as quadriceps weakness, atrophy, and a shift in muscle fiber type towards type II fibers. Functional changes, including reduced muscle strength, endurance, and enzymatic activity, are also prominent features of this dysfunction. Skeletal muscle dysfunction significantly contributes to limitations in exercise capacity and decreased quality of life for individuals with COPD.[6,7]

Notably, COPD patients' respiratory muscles, particularly the diaphragm, differ structurally and functionally from skeletal muscles. This disparity could be the result of different working conditions for these muscles. In COPD patients, lean muscles are often underused, whereas the diaphragm continuously struggles against increasing strain. Several factors play a role in the development of skeletal muscle dysfunction in COPD patients, including a sedentary lifestyle, tissue hypoxia, and systemic inflammation.[6]

Systemic inflammation, influenced by cytokines like TNF-α, oxidative stress, and nitrosative stress, can lead to muscle

dysfunction, atrophy, and apoptosis. COPD patients exhibit elevated circulating levels of these cytokines and inflammatory cells.[6] Muscle atrophy and weakness are found in 30-40% of COPD patients. Those with muscle wasting and fault tend to be sedentary and may become bedridden, exacerbating lung function and the overall COPD condition.[8]

Sarcopenic obesity (SO) is prevalent among patients with COPD, presenting a significant comorbidity that complicates the clinical outcomes of these patients. The condition of sarcopenic obesity combines the characteristics of sarcopenia (loss of skeletal muscle mass and function) and obesity (excess body fat accumulation), each of which independently affects the health status of COPD patients.[9,10]

The pathogenesis of sarcopenic obesity in patients with COPD is multifaceted, involving a complex interplay of systemic inflammation, muscle dysfunction, and metabolic disturbances. The abnormal expression of adipocytokines, such as resistin, is significant in the pathogenesis of sarcopenic obesity in COPD. Resistin plays a crucial role in lipometabolism and has pro-inflammatory effects, which contribute to the complex inflammatory response observed in COPD patients with sarcopenic obesity.[9,10]

## SARCOPENIA IN PATIENTS WITH COPD

In 1989, Rosenberg first described age-related alterations in muscles and pioneered "sarcopenia" to refer to the age-related loss of muscle mass. The term sarcopenia has developed to incorporate muscular atrophy and muscle function.[11] Sarcopenia is the age-related decrease of skeletal muscle mass, which raises the risk of physical disability, deteriorating health, and mortality. It is recognized as a clinical syndrome that includes physical inactivity, malnutrition, and chronic diseases.

The loss of muscle mass in sarcopenia is generally attributed to a combination of muscle atrophy and muscle cell death. At the molecular level, there are changes in protein synthesis and degradation in sarcopenia.[12] Sarcopenia affects both respiratory and non-respiratory muscles. It is influenced by systemic inflammation, oxidative stress, hypoxia, hypercapnia, protein synthesis, catabolic imbalance, nutritional changes, smoking, endocrine dysfunction, aging, and medications like steroids.[13]

Each of these factors, either individually or collectively, leads to muscle mass reduction, cross-sectional area reduction, decreased bioenergetic muscle metabolism (related to fiber type ratio, mitochondrial activity, and muscle blood flow availability), impaired muscle repair, and regeneration mechanisms, along with anatomical and functional pathology (such as apoptosis). These combined effects result in decreased muscle performance.[13] Ongoing research continues to investigate the molecular mechanisms involved in sarcopenia. Reduced muscle mass and impaired muscle function are pivotal components of sarcopenia, initially

characterized as a multifaceted geriatric syndrome.[3]

However, it is now widely acknowledged that muscle impairment can be attributed to various diseases, extending beyond age-related factors. The onset of sarcopenia is multifactorial, involving neurological factors related to motor neuron loss, endocrine factors such as reduced hormone expression (e.g., testosterone and growth hormone), motor unit loss, nutrition, and sedentary lifestyle changes. Inactivity is often accompanied by an imbalance in high saturated fat intake, leading to increased fat deposition in adipose tissue, the liver, and muscles.[3]

In the context of COPD patients, skeletal muscle dysfunction is an independent adverse prognostic factor for lung function.[13] Importantly, extrapulmonary manifestations play a substantial role in the decline of functional capacity among individuals with COPD, and these functional impairments are closely linked to muscle weakness and weight loss.[3]

Sarcopenia in COPD has a detrimental impact, reducing the quality of life and increasing hospitalization rates, mortality, and financial burdens.[13] Recognizing this broader perspective, the European Working Group of Sarcopenia in Older People (EWGSOP2) has underscored the significance of differentiating between "secondary sarcopenia," influenced by factors other than aging, and "primary sarcopenia," which is primarily age-related. Notably, sarcopenia can be induced by underlying diseases such as COPD or other conditions characterized by chronic inflammation.[3]

Based on a Systematic Review and Meta-Analysis by Benz et al, the prevalence of sarcopenia in COPD is 21.6%, with varying rates of 8% in the general population, 21% in clinic-based studies, and 63% among COPD patients in nursing homes.[3] According to a cross-sectional study conducted by Costa et al in 2015 on the relationship between COPD severity and prognosis, the prevalence of sarcopenia was found to be 39.6% (36 out of 91 patients).[14]

Sarcopenia was not associated with GOLD stage or FEV1 results. However, it was more prevalent in COPD patients with Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) index in quartiles 3 and 4 compared to quartiles 1 or 2. Multivariate analysis indicated a significant association between BODE quartiles and sarcopenia, irrespective of age, gender, smoking status, and GOLD stage.[14]

## Sarcopenia Pathogenesis in COPD patients

Sarcopenia in COPD is a result of chronic systemic inflammation. Various molecular pathways contribute to its processes, such as inflammatory mediators, satellite cells, neuronal processes, and hypoxemia. Other mechanisms like muscle dystrophy, glucocorticoids, medications, and disease also contribute to the development of sarcopenia in COPD patients. In patients experiencing muscle decline, it shows

increased levels of TNF-α and IL-6, which are negatively correlated with grip strength and skeletal muscle mass index.[13]

The immune system also plays a crucial role in skeletal muscle regeneration; however, the diminished muscle regenerative capacity found in sarcopenia is caused by local inflammation mechanisms that trigger changes in neurohormonal responses, thus resulting in an imbalance between protein synthesis and degradation, pro-inflammatory cytokines, such. The imbalance between pro- and anti-inflammatory factors results in chronic low-grade pro-inflammatory states progressively damaging muscles.[12] Inflammation also influences skeletal muscle dysfunction through oxidative stress and muscle cell apoptosis.[13]

Aging processes are associated with increased pro-inflammatory cytokines, leading to increased production of acute-phase reactive proteins, immune responses, and immune-senescence or inflammation. As individuals age, the activation of satellite cells significantly decreases or may even halt, influenced by various factors. Moreover, older individuals require more significant stimuli, such as muscle fiber stretching, to activate satellite cells. Consequently, advancing age is closely associated with a notable reduction in actively functioning satellite cells, which can impact muscle regeneration and overall muscle health.[12]

Oxidative stress, a critical factor in diseases like COPD, significantly affects skeletal muscle. Sources include lack of oxygen, inflammation, smoking, environmental pollutants, and increased respiratory rates. These reactive oxygen/nitrogen species ROS/RNS) cause structural and functional alterations, leading to sarcopenia. Understanding this relationship is crucial for developing effective therapeutic strategies to manage sarcopenia in COPD patients.[12,13] Muscle contraction involves brain structures and neurotrophic factors. Brain-derived neurotrophic factor (BDNF), a critical neurotrophic factor, is crucial in muscle fiber metabolism and DNA repair. It is released during skeletal muscle contractions, improving lipid metabolism and muscle fiber function.[12]

Increased physical activity boosts BDNF production, maintaining the central nervous system and skeletal muscle homeostasis. Another neurotrophic factor, insulin-like growth factor I (IGF-1), is essential for protein synthesis and binds to the IGF receptor, preventing protein degradation.[15] These mechanisms are crucial for muscle health and the potential consequences of aging.

The pathomechanism of sarcopenia is closely intertwined with reduced physical activity, creating a detrimental cycle of muscle deterioration. Hyperinflation and the sensation of breathlessness in COPD patients can lead to reduced physical activity. Skeletal muscle disuse can trigger various adaptive changes, including decreased type I fibers and oxidative capacity, muscle fiber atrophy, and muscle capillary density. These changes result in decreased muscle endurance and strength. The reduced strength and endurance of

muscles further limit the mobility of COPD patients, exacerbating problems.[13]

A study found that sedentary healthy individuals have fewer type I muscle fibers in their vastus lateralis muscle than active, healthy individuals. This decrease in muscle endurance is attributed to atrophy of disused muscles, which leads to faster proteolysis and reduced protein synthesis.[13]

Patients with sarcopenia or COPD generally experience a reduction in physical activity; moreover, sarcopenia in COPD patients. All of these ultimately lead to muscle atrophy. Protein breakdown in COPD patients is often caused by a decrease in appetite, age-related anorexia, and muscle-related issues, thus resulting in inadequate energy intake. The breakdown of the protein process thus leads to skeletal muscle atrophy, reduced exercise tolerance, and a lower quality of life for the patients. As malnutrition is prevalent among the majority of COPD patients, nutritional status plays a crucial role in the development of sarcopenia.[13]

## Clinical Impact of Sarcopenia in COPD Patients

Deconditioning due to low activity is a primary cause of significant muscle dysfunction. In COPD, the most dominant muscle atrophy occurs in the leg muscles, particularly the thigh muscles, compared to other muscle groups. In severe COPD, there is a shift from type I to type IIx muscle fibers, which become less efficient in energy output, requiring higher oxygen levels during submaximal workload. Systemic oxidative stress is correlated with quadriceps muscle endurance in severe COPD patients.[11]

In individuals with hypoxemia, there is a higher level of oxidative stress in extremity muscles, leading to decreased quadriceps function. The strength of the quadriceps muscles in COPD patients is typically 20-30% lower than in the average population.[11]

Consequently, COPD patients exhibit significantly lower quadriceps endurance and strength. Many COPD patients complain of leg fatigue, which often leads to exercise termination before experiencing shortness of breath. Weakness in the quadriceps muscles is frequently observed after acute COPD exacerbations, and it takes approximately three months of treatment to restore muscle strength.[11]

## Sarcopenia Assessment

Early detection of sarcopenia in COPD is crucial, given its therapeutic implications for pulmonary rehabilitation and the management of respiratory failure in COPD patients.[14] The Asian Working Group for Sarcopenia (AWGS) 2019 consensus provides a comprehensive approach to diagnosing sarcopenia, which includes assessments of muscle strength, muscle mass, and physical performance. AWGS 2019 consensus defines sarcopenia as losing muscle mass due to aging, low muscle strength, and reduced physical performance.[16]

The Asian Working Group for Sarcopenia determines cut-off values for each diagnostic component based on Asian

research findings. Although sarcopenic characteristics can be found in younger individuals, further investigation of the underlying pathophysiology is needed before diagnosing it as sarcopenia. AWGS supports the early identification of at-risk individuals to enable precise interventions. In the AWGS 2019 guidelines, the diagnosis of sarcopenia requires measuring muscle quantity and quality. It defines severe sarcopenia as having low muscle mass, low muscle strength, and low physical performance.[16]

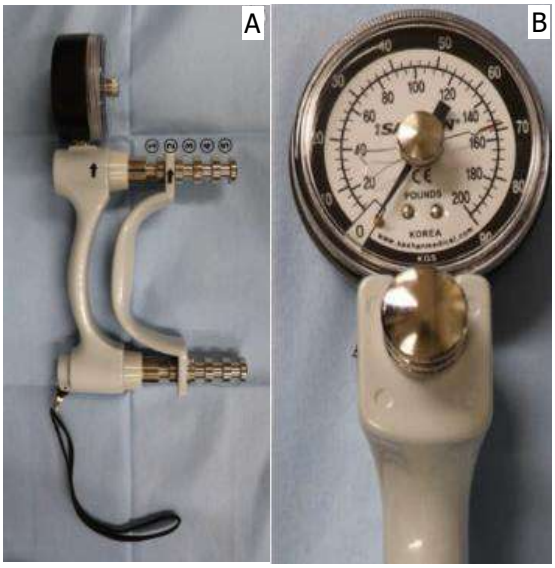


Figure 1. (A) Hydraulic-type dynamometer (Jamar). (B) Jamar showcases the grip strength in either pounds or kilograms, with a maximum limit of 200 pounds or 90 kilograms[17]

Handgrip strength assessment remains recommended for evaluating muscle strength. Asia's most commonly used handgrip dynamometers are the spring-type dynamometer (Smedley) and hydraulic-type (Jamar). AWGS 2019 suggests that muscle strength measurements for sarcopenia evaluation can utilize any equipment if it follows the standardized protocol for each specific model. The proposed method for assessing handgrip strength involves obtaining the highest result from at least two trials using both hands or the dominant hand with maximal isometric contraction effort.[16]

There are various types of physical performance tests: the Short Physical Performance Battery (SPPB), assesses lower-extremity function through tasks like walking, balancing, and chair stands. The usual gait speed test typically involves measuring the time it takes for an individual to walk a specified distance, such as 4 meters, and calculating the speed in meters per second (m/s).[18]


Figure 2. Mechanical type dynamometer (Smedley) (A) Baseline. (B) Takei, GRIP-A[17]

Table 1. Assessment tools recommended by AWGS 2019 for sarcopenia[16]

| Assessment Component | Tool/Method | AWGS 2019 Cut-off Values |
|---|---|---|
| Muscle Strength | Handgrip Strength Test | Men: <28 kg;<br>Women: <18 kg |
| Muscle Mass | • Dual-energy X-ray Absorptiometry (DXA) | Men: <7.0 kg/m²;<br>Women: <5.4 kg/m² |
| | • Bioelectrical Impedance Analysis (BIA) | Men: <7.0 kg/m²;<br>Women: <5.4 kg/m² |
| Physical Performance | • Usual Gait Speed | <1.0 m/s |
| | • Short Physical Performance Battery (SPPB) | Score <9 |
| | • Timed Up and Go Test (TUG) | ≥12 seconds |

The 6-minute walk test measures the distance an individual can walk over a total of six minutes on a hard, flat surface. It assesses the aerobic capacity and endurance of an individual. Stair-climb power test evaluates leg muscle power by measuring the time it takes to ascend a set number of stairs. Timed-up-and-go test assesses mobility, balance, walking ability, and fall risk in older adults by timing how long it takes an individual to stand up from a chair, walk a short distance, turn around, walk back to the chair, and sit down.[18]

The 5-time chair stand test (5-CST) measures lower limb muscle strength by timing how quickly an individual can rise from a chair and sit down five times without using their arms. Poor performance in the 5-CST indicates reduced lower limb muscle strength and has been recommended for use in the initial assessment of sarcopenia.[18]

## REHABILITATION MANAGEMENT SARCOPENIA IN COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) includes physical activity as a non-pharmacological intervention in managing stable COPD.[1] GOLD emphasizes that non-pharmacological management complements pharmacological treatment and is integral to comprehensive COPD management.[16] Besides that, AWGS recommends the importance of intervening in sarcopenia in patients with or without underlying clinical conditions.[12]

To date, there is no curative therapy for sarcopenia, and the current management strategy aims to delay its onset and reduce symptoms, primarily through physical activity. Sedentary lifestyles in elderly patients lead to skeletal muscle inactivity, accelerating muscle strength loss and muscle atrophy. By controlling various variables, including oxidative stress, neuronal dysfunction, and inflammation, exercise can offset the detrimental effects that contribute to sarcopenia.[12]

The physical medicine and rehabilitation management benefits for COPD patients with sarcopenia include improvements in skeletal muscle mass and strength, which can halt or even reverse

the progression of muscle loss. Rehabilitation can also alleviate the disease burden and improve the quality of life for these patients. Pulmonary rehabilitation has been shown to reverse sarcopenia in patients with low skeletal muscle mass and improve exercise capacity, functional performance, limb strength, and health status.[8]

As part of a rehabilitation program, regular exercises are an effective strategy for protecting against sarcopenia in COPD patients, as they can increase muscle mass and strength. Additionally, nutritional supplements combined with exercise have been found to improve the performance of patients with coexisting COPD and sarcopenia. Pulmonary rehabilitation (PR) programs for COPD patients with sarcopenia can vary in duration and intensity, tailored to the individual's capabilities, and may include both aerobic and resistance training components.[8]

## Exercise

Pulmonary rehabilitation in COPD patients has demonstrated its effectiveness, offering tangible benefits supported by high-quality scientific evidence. The primary objective of pulmonary rehabilitation is to enhance exercise capacity, alleviate breathlessness, and improve the quality of life for patients. Pulmonary rehabilitation represents an integrated multidisciplinary management program encompassing exercise, education, behavior modification, and nutritional therapy.[11,19]

Exercise is recognized as one of the most productive approaches to addressing sarcopenia. EWGSOP endorses exercise as the primary intervention for sarcopenia, intending to enhance physical performance, strength, and muscle mass.[11]

## Exercise-induced molecular remodeling

Sarcopenia exercise programs comprise multimodality, including strength-resistance, aerobic exercise, balance, and flexibility training, in which strength training stands as the frontline intervention for managing sarcopenia.[20] Exercise benefits sarcopenia patients through multiple molecular pathways, including antioxidant alteration, reduction of myostatin expression, activation of satellite cells, and positive effects on telomere length, ultimately preserving muscle strength and function. Physical exercise induces alterations in antioxidant enzyme levels in acute and long-term scenarios.[12]

These changes are prompted by ROS generated during exercise, pivotal in muscle adaptation to decelerate sarcopenia. Consequently, post-exercise ROS in muscle cells can act as numerous genes' activators or suppressors. Skeletal muscles can adapt to specific stimuli or stressors induced by concentric or eccentric muscle contractions, stretching, or contraction.[12] Strength or resistance training provides relief to the issues of muscular atrophy and weakness, which have been fundamental components of sarcopenia.[21] Not only does strength training improve muscle strength and

quality of life, but also beneficial to increase the exercise capacity of COPD patients.[21]

Furthermore, to boost muscle strength efficiently, it is recommended to do multi-joint exercises.[21] Resistance training is less aerobic and oxidative than aerobic exercise, as it increases nitric oxide levels and NO synthase (NOS), indirectly shielding muscles from pro-oxidant effects. This promotes antioxidant defenses and reduces inflammatory pathways during exercise. This evidence underscores the foundation and management of muscle abnormalities resulting from aging, emphasizing the importance of physical exercise and nutritional intake.[12]

Exercise can be a double-edged sword for sarcopenia patients. While it can help improve muscle strength and function, it may also increase myostatin expression in muscle fiber, a factor associated with muscle wasting. In sarcopenia exercise, the increase in myostatin expression is often accompanied by a parallel enhancement in the activation and proliferation of satellite cells, representing a complex interplay within the muscle microenvironment.[12]

The activation of satellite cells is triggered by nitric oxide (NO) produced by NOS in quadriceps muscles during active but not passive exercise. Resistance training enhances the activation and proliferation of satellite cells. There is an increase in satellite cells in skeletal muscles by 19% after 30 days of resistance training and 31% after 90 days of resistance training.[12]

Changes in satellite cells following adaptation to exercise are associated with decreased oxygen levels in muscle cells and increased vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), which can influence satellite cell proliferation induced by resistance training. In addition, regular resistance training and moderate oxidative stress positively affect telomere length in leukocytes and skeletal muscles. There is strong evidence that satellite cell activity is crucial in delaying sarcopenia as a response to exercise adaptation, maintaining muscle strength and functionality.[12]

## Skeletal Muscle Adaptation in Resistance Exercise

Exercise induces the remodeling of skeletal muscles, supported by acute and chronic genetic alterations and protein production. Skeletal muscles are highly plastic tissues capable of adapting to minor nutrition and contractile activity alterations. Resistance exercise significantly stimulates the rate of muscle protein synthesis (MPS) with only minimal impact on muscle protein breakdown (MPB) rates.[22]

Combining resistance exercise with protein intake results in an increased rate of MPS in skeletal muscle proteins, ultimately leading to muscle hypertrophy. Dynamic stimulation of skeletal muscles with low-intensity, repetitive, and prolonged loads (as seen in endurance training) enhances the expression of mitochondrial genes, proteins, and mitochondrial content, shifting towards an oxidative phenotype and increasing resistance to fatigue.[22]

Resistance exercise stimulates gene transcription and accelerates the synthesis of new muscle proteins. During prolonged exercise, a transcriptional response, protein synthesis response, and proteomic changes result in muscle hypertrophy and an oxidative phenotype. The biological basis of exercise-induced skeletal muscle phenotype changes lies in the repeated stimulation of increased mRNA expression, leading to enhanced protein translation and adaptive alterations in muscle protein content.[22]

One gene transcription induced by resistance exercises was found in the mechanistic target of rapamycin complex 1 (mTORC1). Its activation enhances muscle protein synthesis through the downstream activation of proteins such as ribosomal protein 70-kDA S6 kinase 1 (p70S6K1) and 4E-binding protein-1 (4EBP1), which initiate ribosome binding to mRNA for protein synthesis initiation. Therefore, resistance exercise stimulates mTORC1 activity, leading to increased rates of myofibrillar protein synthesis through enhanced translation efficiency (protein synthesized per unit mRNA) and translation capacity (ribosome quantity).[22]

## Endurance training

Exercise-induced mitochondrial biogenesis is a characteristic of endurance training. It is supported by increased regulation of mitochondria and coordinated nuclear transcription encoding proteins involved in the electron transport chain and fatty acid metabolism. These transcriptional processes include peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, nuclear respiratory factors (NRFs), and mitochondrial transcription factor A (TFAM). Endurance training over an extended period elevates mRNA expression of PGC-1α. Endurance exercise results in highly coordinated mitochondrial adaptations (from mRNA to protein) that are time-dependent (ranging from hours to days).[22]

## Impact of exercise repetitions

When combined with protein intake, skeletal muscles enter a positive protein balance shortly after exercise. Changes in the cross-sectional area (CSA) of skeletal muscle fibers are only minimally detected through photochromic staining after 6-7 weeks of exercise. An increase in total RNA and 45S pre-rRNA occurs after 3 weeks and 6 weeks of resistance exercise, with this expression returning to baseline levels after 2 weeks of resistance exercise.[22]

Resistance exercise over 20 weeks shows that individuals with the highest muscle hypertrophy display increased rRNA expression. Furthermore, muscle protein synthesis (MPS) increases within a few hours after resistance exercise and skeletal muscles remain responsive to anabolic influences 24-48 hours after protein intake. The early-phase elevation in MPS during post-resistance exercise recovery indicates the remodeling of contractile and structural proteins.[22]

Resistance exercise induces skeletal muscle contractions using external resistance, such as dumbbells, elastic therapy bands, and the patient's body

weight.[20] In general, resistance training can begin with a load of 50-60% of the one-repetition maximum (1RM) for 12-15 repetitions.[11]

Evaluation of improvement in muscle strength should be conducted routinely; therefore, the exercise intensity can be gradually increased with a frequency of 1 to 3 sets per day. Resistance training, especially for thigh muscles, is crucial for daily activities such as standing and walking, and weakness in thigh muscles can lead to physical inactivity. Although intensive resistance training in elderly patients has proven effective in enhancing muscle function and mass, it is recommended to gradually increase the intensity of progressive overload training to prevent musculoskeletal injuries.[11]

Intensive resistance training in elderly patients has proven effective in enhancing muscle function and mass. However, it is recommended to gradually increase the intensity of progressive overload training to prevent musculoskeletal injuries.[11,20] The effects of resistance training in older patients include muscle hypertrophy, increased muscle strength, and improved physical performance. High-intensity resistance training is more effective for sarcopenia than home-based exercises or exercises with light resistance.[12]

However, a 6-month home-based exercise program that combines walking and resistance exercises for the lower extremities (such as squats, single-leg standing, and heel raises) is efficacious in improving maximum walking speed and muscle strength in patients aged 60 or older with sarcopenia or low muscle mass.[12]

Resistance training is recommended 2 to 3 days per week, combined with aerobic exercise to maintain cardiovascular function. It is advised to incorporate 1 day of rest and mental recovery. Resistance and endurance exercises should be adapted to each patient's recommendations and exercise protocols, considering motor limitations, intensity, and duration.[12]

The recommendations provided by Cruz-Jentoft et al. suggest supervised resistance training or exercise programs for sedentary or frail patients. The intervention should last at least 3 months or longer to achieve significant clinical outcomes, particularly in muscle strength and physical performance. Although Cruz-Jentoft et al. found that resistance exercise increases muscle strength and physical performance but does not significantly affect muscle mass.[23]

Aerobic or endurance exercise prevents muscle loss and is effective with resistance training.[8] Endurance exercise improves hyperinflammation conditions induced by exercise. It reduces exertional dyspnea, heart rate recovery, and muscle dysfunction in COPD patients.[21]

Common exercise modalities include walking on the ground or on a treadmill and static cycling. Patients with COPD often experience breathlessness and quad muscle fatigue after cycling or walking; ground walking could enhance walking capacity. Upper extremity exercises are

also advised for COPD patients, such as aerobic arm cycle ergometer training targeting muscles like the biceps, triceps, deltoids, latissimus dorsi, and pectoralis.[21] Furthermore, balance training is crucial for patients, especially older individuals, to improve postural control.[11]

One consideration when prescribing exercise for COPD patients is the decreased respiratory function, which then poses a risk for exercise-induced desaturation (EID) in severe and very severe COPD patients with an FEV1 <50%. A SpO2 saturation <90% that remains uncorrected indicates terminating exercise. If EID is identified, adequate oxygenation should be provided during exercise. It is advisable to exercise indoors to prevent exposure to air pollution and fine particles that may trigger acute exacerbations.[11]

**High-Intensity Interval Exercise**

High-intensity interval exercise (HIIE) improves cardiorespiratory fitness and stimulates mitochondrial biogenesis in muscles. HIIE notably impacts muscle protein remodeling and hypertrophy by increasing muscle protein synthesis (MPS), particularly mitochondrial protein synthesis, and inducing fibrillar protein remodeling.[22]

An increase in the number of differentiated satellite cells has been observed after HIIE, indicating the role of satellite cells in muscle fiber remodeling. HIIE training enhances the number of satellite cells associated with hybrid muscle fibers, supporting the idea that HIIE plays a role in triggering muscle fiber remodeling.[22]

**Exercise prescription**

To prescribe exercise for COPD patients with sarcopenia, a comprehensive approach that includes targeted exercise training and aerobic and strengthening exercises, alongside adequate protein and caloric intake and micronutrient management, is recommended.[8]

The exercise type should be a combination of aerobic and resistance training, starting 3 times per week and aiming for 5 times as tolerated. The intensity should be based on perceived effort, heart rate, and exercise capacity, 4 to 12 weeks, with 60 to 90-minute sessions. This exercise prescription should be personalized to each COPD patient with sarcopenia, considering their current health status, exercise tolerance, and nutritional needs.[8]

**Exercise Precautions**

Research by Sahin and Naz on the demographic and clinical characteristics of COPD patients who failed to complete an 8-week PR exercise program found that patients with a history of smoking and severe COPD were the most common non-completers, often due to a lack of motivation (49%), transportation problems (23.8%), exacerbations (18.4%), work-related reasons (4.8%), and hospitalization (4.1%). This underscores the importance of healthcare professionals providing clear information and maintaining a positive attitude while interacting with patients.[24]

## ASSESSMENT METHODS FOR COPD PATIENT EXERCISE

Patient assessment and program outcomes are crucial components of patient exercise programs. It is essential to assess the patient's condition before starting an exercise regimen, including symptoms, endurance, strength, quality of life, and other relevant factors. These assessments should be conducted before, during, and after exercise to evaluate effectiveness. Breathlessness is the most commonly reported symptom by COPD patients. Identifying and evaluating the patient's symptoms before, during, and after exercise is vital to guide their exercise regimen.[21]

## NUTRITIONAL THERAPY

Malnutrition increases the risk of weight loss and has implications for the development of sarcopenia. In conditions of calorie deficit, protein becomes the primary source of energy; consequently, a combination of adequate nutritional and additional protein intake. Research has shown a positive correlation between protein intake and muscle mass. A study involving 2,066 elderly patients found that the group with a protein intake of 1.2 g/kg had lower muscle mass loss than the group with an infusion of 0.8 g/kg. The PROT-AGE study group recommends a protein intake of 1.2–1.5 g/kg for elderly individuals with acute or chronic diseases.[11]

Omega-3, healthy fats, and hydration are also essential for individuals with sarcopenia.[20] Significant clinical improvements have been noted in mid-arm circumference, fat-free mass index (FFMI), results of the 6-minute walk test, respiratory muscle strength, and quality of life when providing nutritional supplementation to malnourished COPD patients.[11]

## MEDICATION

Several medications and supplements are known to be beneficial for COPD patients with sarcopenia. Vitamin D plays a crucial role in muscle metabolism, the formation of skeletal muscle mass, and muscle strength. Type II muscle fiber atrophy may occur in cases of vitamin D deficiency. Type II muscle fibers play a role in preventing falls through fast-twitching; therefore, vitamin D supplementation can reduce the risk of falling. Sarcopenic patients with low vitamin D levels (<20 ng/mL based on the 25-hydroxyvitamin D test) should receive vitamin D supplementation. Beta-hydroxy-β-methyl-butyrate (HMB) is a metabolite of leucine often used as a nutritional supplement in muscle training. HMB enhances protein synthesis through protective and anti-catabolic effects, stabilizes muscle cell membranes, and reduces proteolytic pathways, lowering sarcopenia. In COPD, HMB is known to prevent muscle loss, with a standard dose of 3 grams/day of HMB.[11]

## THE ROLE OF CIRCADIAN RHYTHMS IN SARCOPENIA

Recent evidence suggests that circadian timing plays a role in triggering

skeletal muscle growth and maintaining body homeostasis. Generally, circadian rhythms are regulated by light-dark cycles, but physical activity also modulates these rhythms. Thus, preserving biological rhythms is essential for preventing and delaying sarcopenia.[12]

## CONCLUSION

Chronic Obstructive Pulmonary Disease (COPD) causes systemic inflammation, affecting both respiratory and non-respiratory muscles, leading to muscle loss and sarcopenia. Sarcopenia is influenced by neurological, endocrine, and nutritional factors. It can lead to decreased quality of life, increased hospitalization rates, mortality, and financial burdens. Sarcopenia assessment should follow AWGS 2019 guidelines and include skeletal muscle mass strength, physical performance, and appendicular skeletal muscle mass.

Pulmonary rehabilitation represents an integrated multidisciplinary management program encompassing exercise, education, behavior modification, and nutritional therapy. Exercise is the primary treatment for sarcopenia, as there is no curative therapy available. Strength resistance, aerobic exercise, balance, endurance training, and flexibility training can enhance physical performance, strength, and muscle mass are the most suitable program compositions. Motivation is also crucial for adherence to exercise programs and maintaining the exercise engram. Proper nutrition, protein intake, and vitamin D supplementation may also be beneficial.

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