Original Article

Factors that Affected the Mortality Rate of Chronic Obstructive Pulmonary Disease Patients with Respiratory Failure

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a significant health issue with high morbidity and mortality rates. However, risk factors for COPD, particularly in cases with type II respiratory failure, are not fully understood. This study analyzes factors influencing the mortality rate of COPD patients with type II respiratory failure.

Methods: This observational study used a cross-sectional design, analyzing medical records of COPD patients with type II respiratory failure treated at H. Adam Malik General Hospital, Medan, from November 2021 to September 2022. A total of 42 patients met the inclusion criteria. Data analysis included descriptive statistics and inferential tests using the Chi-Square test and multiple logistic regression to identify the most dominant factors.

Results: Among the 42 patients, the mortality rate was 50%. Variables such as gender, age, number of comorbidities, smoking habits, and history of exacerbations were not significantly associated with mortality. Patients who did not regularly use inhalers had a 19-fold higher mortality risk than those who did (*P*=0.004; OR=19.79; 95% CI=2.67-146.99). Length of stay was inversely associated with mortality, with each additional day reducing the risk by 0.77 times (*P*=0.011; OR=0.77; 95% CI=0.63-0.94).

Conclusion: Routine inhaler use and length of stay are significant factors influencing the mortality rate in COPD patients with type II respiratory failure.

Keywords: COPD, inhaler therapy, length of stay, mortality, type II respiratory failure

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a very important international health problem. The prevalence of COPD in Europe is estimated at 4% to 10%.[1] By 2022, more than 3 million people will die from COPD, with the global burden expected to increase in the coming decades, highlighting the significant impact this disease has on mortality worldwide.[2] The Global Initiative for COPD (GOLD) defines COPD as “a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.[2]

Factors that affect the development of COPD are genetics, environmental exposure and work, socioeconomic factors, age, gender, and lung growth and development. The pathogenesis of COPD involves oxidative stress, protease-antiprotease imbalance, mediators and inflammatory processes, and other pathophysiological changes.[3] In mild and moderate COPD, lung cancer and cardiovascular disease are Chronic obstructive respiratory disease (COPD) accounts for about 83% of the four million deaths caused by chronic respiratory diseases globally. This makes COPD a significant cause of death.[4]

Research by Carone et al. has shown that age, forced vital capacity, oxygen flow at rest, and disease-specific health status are independent predictors of death in patients with COPD and chronic respiratory failure. Other physiological factors, such as exercise performance, are not associated with a three-year survival of COPD patients.[5] Meanwhile, Anggraeni et al reported that a history of exacerbation within the previous year was

an independent risk factor for the occurrence of respiratory failure in acute exacerbation of COPD patients.[6]

This study aims to analyze the factors affecting the mortality rate of COPD patients with respiratory failure, focusing on patient demographic characteristics and the influence of these characteristics on clinical outcomes.

METHODS

This research was an observational study with a cross-sectional design, using medical records data of COPD patients with type 2 respiratory failure being treated at H. Adam Malik General Hospital Medan. It was carried out over 11 months, from November 2021 to September 2022.

The minimum sample size to evaluate the hypothesis of a different proportion was 42 patients. The variables measured were patient characteristics such as gender, age, comorbidities, total comorbidities, smoking habits, use of inhaler therapy as prescribed per 12 hours, exacerbation history in 6 months, length of treatment, and the outcome of patient care in the form of hospital discharge or death. The inclusion criteria included patients diagnosed with acute exacerbation of chronic obstructive pulmonary disease and type II respiratory failure based on clinical symptoms and blood gas analysis results. In contrast, the exclusion criteria were incomplete medical record data and patients diagnosed with severe COPD, for example, COPD that is exacerbating.

Research data were processed using statistical software. The data collected were processed and analyzed descriptively to determine the frequency distribution of research subjects based on characteristics; and then, proceeded with inferential analysis. The bivariate analysis of the relationship between independent and dependent variables was performed using the chi-square test. To obtain the most dominant independent variable effect on the dependent variable, multiple logistic regression tests was used. The significance level was obtained if the value of $P<0.05$.

RESULTS

This research was conducted on 42 patients diagnosed with COPD and type 2 respiratory failure at Haji Adam Malik General Hospital Medan from November 2021 to September 2022.

Table 1. Demographic characteristics of research subjects (n=42)

Demographic Characteristics	n (%)
Gender	
Male	33 (78.6%)
Female	9 (21.4%)
Age	
≥60 years old	20 (47.6%)
<60 years old	22 (52.4%)
Comorbidity	
CHF	1 (2.4%)
CKD and Type 2 DM	1 (2.4%)
Type 2 DM	2 (4.8%)
Hypertension	3 (7.1%)
Hypertension and Type 2 DM	3 (7.1%)
Hypertension and SOL	1 (2.4%)
Pneumonia	1 (2.4%)
Pneumonia and CKD	3 (7.1%)
Pneumonia and Type 2 DM	6 (14.3%)
Pneumonia and ICH	1 (2.4%)
Pneumonia and Stroke	1 (2.4%)
SOL	1 (2.4%)
SOL and Type 2 DM	1 (2.4%)
Stroke	2 (4.8%)
Stroke and CHF	2 (4.8%)
Stroke and Type 2 DM	1 (2.4%)
Stroke and Ensefalopati	1 (2.4%)
Stroke and Hipertensi	4 (9.5%)
TB pulmonal	5 (11.9%)
TB pulmonary and Type 2 DM	1 (2.4%)
None	1 (2.4%)
Total comorbidity	
0	1 (2.4%)
1	15 (35.7%)
2	26 (61.9%)
Smoking habit	
Active Smokers	17 (40.5%)
Former Smoker	17 (40.5%)
Not a Smokers	8 (19.0%)
Inhaler therapy	
Not routine	18 (42.9%)
Routine	24 (57.1%)
History of exacerbation	
>1x in 1 year	27 (64.3%)
1x in 1 year	1 (2.4%)
None	14 (33.3%)
Length of stay	
Mean±SD	9.6±5.82
Median (Min-Max)	8.5 (2-25)
Outcome	
Death	21 (50.0%)
Survive	21 (50.0%)

All samples met the inclusion criteria. Most of the patients (78.6%) were male. There were 22 patients (52.4%) aged <60 years. The most common types of comorbidities were pneumonia and type 2 diabetes mellitus (DM) for as many as six people (14.3%). The number of patients with two comorbid diseases was 26 (61.9%).

A total of 17 patients were active smokers and former smokers. As many as 18 patients (42.9%) did not use inhaler therapy routinely. Most of the subjects experienced exacerbations >1 time in a year. Patients' mean length of stay was 9.6 days, with the shortest length of stay of 2 days, and the longest of 25 days. A total of 21 patients died.

Variables of gender, age, number of comorbidities, smoking habits, and history of exacerbations were not correlated with mortality rates of COPD patients (*P*>0.05). Out of the 18 patients who did not use inhalers regularly, 15 people (83.3%) died. Meanwhile, out of 24 patients who used inhalers regularly, only six people (25%) died.

The chi-square test pointed out a significant correlation between routine inhaler use and mortality in COPD patients with type 2 respiratory failure (*P*<0.001). The median length of stay in patients who died was 4 days, and the median length of stay in patients who survived was 12 days. Mann-Whitney test results showed a significant correlation between length of stay and mortality (*P*<0.001).

Table 2. Relationship between Gender, Age, Number of Comorbidities, Inhaler treatment, and Length of stay towards Mortality rates in COPD Patients with Type II Respiratory Failure 2

Demographic Characteristics	Death	Survive	*P*
Gender			
Male	19 (57.6%)	14 (42.4%)	0.130[a]
Female	2 (22.2%)	7 (77.8%)	
Age			
≥60 years old	11 (55.0%)	9 (45.0%)	0.537[b]
<60 years old	10 (45.5%)	12 (54.5%)	
Total comorbidity			
0	0 (0%)	1 (100%)	
1	9 (60.0%)	6 (40.0%)	0.425[c]
2	12 (46.2%)	14 (53.8%)	
Smoking habit			
Active Smokers	10 (58.8%)	7 (41.2%)	
Former Smoker	9 (52.9%)	8 (47.1%)	0.283[c]
Not a Smokers	2 (25.0%)	6 (75.0%)	
Inhaler therapy			
Not routine	15 (83.3%)	3 (16.7%)	<0.001[b]
Routine	6 (25.0%)	18 (75.0%)	
History of exacerbation			
Yes	12 (42.9%)	16 (57.1%)	0.190[b]
No	9 (64.3%)	5 (35.7%)	
Length of stay, Median (Min-Max)	4 (2-20)	12 (5-25)	<0.001[d]

Note: [a]Fischer's Exact, [b]Chi Squre, [c]Kruskal Wallis, [d]Mann Whitney

By using the enter method, namely by removing one by one the independent variables starting from the variable with the highest value of *P*>0.05, it was found that only two independent variables had a significant effect on the mortality rate of COPD patients, namely routine use of inhaler therapy (*P*=0.004) and length of stay (*P*=0.011).

Table 3. Multivariate Analysis of Factors that Affected Mortality of COPD Patients with Type II Respiratory Failure

Variable	B	*P*	OR	95% CI
Selection I				
Gender	2.460	0.089	11.701	0.685-199.972
Inhaler Therapy	3.526	0.009	33.979	2.455-470.383
History of exacerbation	-0.476	0.664	0.621	0.073-5.318
Length of stay	-0.228	0.026	0.796	0.651-0.973
Constant	-0.703	0.711	0.495	---
Selection II				
Gender	2.445	0.088	11.526	0.695-191.152
Inhaler Therapy	3.655	0.005	38.670	3.003-498.034
Length of stay	-0.229	0.027	0.795	0.649-0.974
Constant	-1.073	0.527	0.342	---
Selection III				
Inhaler Therapy	2.985	0.004	19.791	2.665-146.994
Length of stay	-0.260	0.011	0.771	0.631-0.942
Constant	1.335	0.184	3.802	---

The variable that most dominantly influenced mortality was routine therapy, with the largest OR=19.791 (95% CI=2.665-146.994), meaning that COPD patients who did not routinely use inhaler therapy would tend to be at risk of experiencing mortality 19.791 times greater than patients who regularly used inhaler therapy.

For the length of stay variable, the value of OR=0.771, meaning that the longer the COPD patient with type 2 respiratory failure was treated, the chance of experiencing mortality will decrease, or for every 1 day of hospitalization, the chance of dying will be 0.771 times.

Factors influencing mortality are routine use of inhaler therapy and length of stay. Patients who do not routinely use inhaler therapy tend to be more at risk, with a mortality rate that is 19 times greater than patients who use inhaler therapy regularly. In addition, the longer the stay, the lower the risk of experiencing mortality.

DISCUSSION

COPD was the third leading cause of death worldwide in 2015 when as many as 3.2 million people died due to this pathological condition.[7] COPD is a global health problem, and according to the World Health Organization (WHO), it is the fourth leading cause of death globally.[8] COPD is characterized by irreversible airflow limitation, which causes persistent and progressive respiratory symptoms, including shortness of breath, coughing, and phlegm. Acute exacerbations of COPD are generally life-threatening, with high in-hospital mortality rates ranging from 11.5–24%. High in-hospital mortality rates of up to 17% are observed in COPD patients with acute respiratory failure.[9]

Type 1 (hypoxemic) respiratory failure is a PaO_2 level <60 mmHg with normal or subnormal $PaCO_2$ levels. In these conditions, gas exchange failure occurs at the alveolar-capillary membrane level, as seen in non-cardiogenic or carcinogenic pulmonary edema and severe pneumonia. Meanwhile, type 2 respiratory failure (hypercapnic) is defined as $PaCO_2$ levels >50 mmHg, and PaO_2 levels can be within normal limits or low in respiratory pump failure conditions.[10]

This research found that gender, age, comorbidity, and smoking history were not significantly correlated to mortality rate, but men aged >60 years with a history of smoking had a higher mortality. The history of patients who had more than one comorbidity also described higher mortality; patients with only one comorbidity in this research also had a high mortality rate due to non-routine use of inhaler therapy.

Consistent with this research, Hedsund demonstrated that COPD patients requiring mechanical ventilation were younger (68 vs. 80 years, P<0.001), with a male predominance (48% vs. 28%, P=0.01) and less likely to receive long-term oxygen therapy (12% vs. 28%, P=0.004).[8]

In contrast with this research, studied by Chen et al. over eleven years with a total of 173 patients with acute respiratory failure who required mechanical ventilation and were admitted to the ICU obtained that among these patients, the mean patient age was 92.1±2.2 years (range: 90-99 years). Most patients were female (n=92, 53.2%).[11]

Chronic obstructive pulmonary disease has been reported to be associated with infection, exposure to cigarette smoke, inhalation of harmful dust and gases, and genetic factors. In addition, chronic inflammation in airways, lung parenchyma, and pulmonary vessels triggers characteristic changes in COPD. It suggests a role for inflammation and inflammatory cytokines in the pathogenesis of COPD. It is strongly associated with male patients due to a history of smoking and exposure to noxious gas dust.[12]

As a chronic systemic inflammatory disease, COPD is associated with various morbidities, including cardiovascular disease, lung cancer, gastroesophageal reflux, bronchiectasis, metabolic syndrome, diabetes, obstructive sleep apnea, osteoporosis, depression/anxiety, and cognitive impairment.[9] The most common comorbidities in this research were pneumonia and type 2 DM in as many as six people (14.3%). The number of patients with two comorbid diseases was 26 people (61.9%).

Judging from the data in this research, the mortality of patients who did not have a comorbidity was low, and those who had a comorbidity had a higher mortality.

Durão et al evaluated the coexistence of diseases contributing to chronic hypercapnic respiratory failure in COPD patients. They found that the majority (81.7%) had one or more respiratory or non-respiratory comorbidities. Obstructive Sleep Apnea (OSA) was found in 54 (49.5%) patients, obesity in 40 (36.7%) patients, heart failure in 25 (22.9%) patients, bronchiectasis in 24 (22.0%) patients, other post-tuberculosis sequelae in 9 (8.3%) patients, lung cancer in 8 (7.3%) patients, and heterogeneous respiratory and non-respiratory diseases in 7 (6.4%).[13] The most frequent morbidities observed in COPD patients in a study by Ho et al were hypertension (65%), coronary artery disease (37%), and stroke (32%).[14]

Smoking is linked to COPD in the majority of cases, but environmental pollution has also had a role. The smoking rate in the Akbaş study was 64%, with the amount of as much as 68±44 pack-years, and other patients were exposed to indoor/outdoor air pollution, such as stoves for heating homes, exposure to second-hand smoke, and using a tandoor oven for baking.[15]

The majority of patients in this research, as many as 17 patients each, were active smokers and former smokers. An estimated 2 million COPD patients are undiagnosed and untreated. Failure to diagnose is not limited to minor illnesses. More than half of patients with moderate-severe disease were misdiagnosed, and 20% of those who were undiagnosed progressed to severe or very severe disease. As many as 10% of emergency admissions for acute exacerbations of COPD are patients with misdiagnosed COPD.[16]

This research showed that most subjects experienced exacerbations more than once a year. Patients' mean length of stay was 9.6 days, with the shortest stay being 2 days and the longest being 25 days. A total of 21 patients died. However, from the results of this research, a history of exacerbations was not included as a significant factor that aggravated mortality in COPD patients with type 2 respiratory failure.

This research found that the median length of stay of patients who died was 4 days, and the median of patients who survived was 12 days. The Mann-Whitney test showed a significant correlation between length of stay and mortality (P<0.001). For every 1 day of hospitalization, the chance of dying is 0.771 times. The proportion of patients who died and survived was equal, namely 21 people (50%) each.

Therapeutic adherence to treatment is one of the most important factors for disease management, and its failure should be considered a major cause of suboptimal response to treatment. Suboptimal adherence can lead to unfavorable disease outcomes, including hospitalization and poor quality of life. COPD treatment adherence rates reported in studies are between 16.0% and 67.0%.[17]

As many as 18 patients (42.9%) did not use inhaler therapy routinely. Of the 18 patients who did not use inhaler therapy routinely, 15 (83.3%) died. Meanwhile, out of 24 patients who used inhaler therapy routinely, only 6 (25%) died. In this research, it was found that the factor that affected mortality was the routine use of inhaler therapy, where patients who did not use inhaler therapy routinely were more at risk, with a mortality rate 19 times greater than patients who used inhaler therapy routinely.

Chi-square test results showed a significant correlation between the routine use of inhaler therapy and mortality in COPD patients with type 2 respiratory failure (P<0.001). The factor that influenced mortality was the routine use of inhalers, meaning that patients who did not use inhaler therapy routinely tended to be at risk of experiencing mortality 19 times greater than patients who used inhaler therapy routinely.

According to 2023 GOLD, COPD patients with clinical symptoms that describe Group A COPD must be given a bronchodilator. Then, in COPD Group B, two bronchodilators are given at once; in COPD Group E, bronchodilators and ICS inhalers are given to be controllers.[18] Inhaled corticosteroid (ICS)/LABA/LAMA FDCs are characterized by mechanisms that provide benefits in reducing

exacerbations, improving lung function and improving health status, and reducing the risk of death (compared to the use of single-dose bronchodilator).[19]

To reduce mortality in COPD patients, reduce the economic and clinical burden, and improve quality of life, the priority management is to prevent disease progression, reduce exacerbation rates, and focus on managing comorbidities. Adherence to inhaler therapy has a significant impact on treatment goals.[20]

In the IMPACT study of inhaler use in three treatment arms, LIPSON et al. reported a significant reduction in mortality in COPD patients at high exacerbation risk (55% of patients with >2 moderate or severe exacerbations and 26% had >1 severe exacerbation in the past year) receiving combination LABA/ICS or LABA/LAMA/ICS therapy compared with dual LABA/LAMA combinations. In both studies, lower mortality was seen despite an increased risk of pneumonia in the ICS-containing therapy group.[21]

Vestbo found that the correlation between adherence to inhaler therapy and mortality remained unchanged and statistically significant after adjusting for other factors associated with prognosis (hazard ratio=0.40, 95% CI=0.35-0.46; *P*<0.001). The correlation was even stronger when analyzing only treatment-related deaths. Similarly, the relationship between adherence and length of stay remained unchanged and was significant in the multivariate analysis (rate ratio 0.58; 95% CI=0.44–0.73; *P*<0.001). The treatment effect was more pronounced in patients with good adherence than in patients with poor adherence. Adherence to inhaled medication was significantly associated with a reduced risk of death and hospital admission due to COPD exacerbations.[22]

The survival rate of these patients is improved by long-term oxygen therapy (LTOT). LTOT has also increased survival by approximately 3.5 years in hypoxemic COPD patients. Still, survival is worse if there is more severe airflow limitation when oxygen therapy is started. In a 2-year study of 140 patients with severe hypercapnic COPD, the two-year survival rate was higher in mechanically ventilated patients compared to non-ventilated patients (1 year, 87.7% versus 56.7%; 2 years, 71.8% versus 42%; *P*=0.001).[5]

LIMITATION

The limitations of this research include the observational nature of the retrospective cohort design using medical records data of COPD patients with type 2 respiratory failure. However, another weakness in this research was that no data was obtained about the use of inhaler drugs consumed by patients; therefore, this research does not have data on inhaler drugs consumed by patients and a clear history of exacerbations to find out what phenotype is most often found in COPD patients with type 2 respiratory failure.

CONCLUSION

Factors that affect the mortality rate of COPD patients with type 2 respiratory failure are routine use of inhalers and length of stay.

CONFLICT OF INTEREST

There are no conflicts of interest.

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