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Original Research

Factors affecting the outcomes in stable chronic obstructive pulmonary disease patients at an Army Central Hospital

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Abstract

Background: Of the four Asian countries, Indonesian COPD patients have the worst clinical features, which puts them at a high risk for treatment failure. There are a number of variables and patient traits that influence clinical results as a predictor of therapy outcomes. **Objective:** to identify the contributing components and how much they influence COPD patients' therapy results. **Methods:** This cross-sectional descriptive-observational study at a tertiary army hospital involved 74 patients. A questionnaire and medical records were utilized to obtain sociodemographic characteristics and clinical data. Correlation and logistic regression analysis were conducted to identify significant factors. **Results:** The results showed that tumor/cancer comorbidities affected the worsening of CAT values (OR=10.89, 95%CI=1.01-117.23, p=0.049), use of ICS/LABA drugs affected the improvement of mMRC values (OR= 0.26, 95%CI=0.08-0.84, p=0.024), history of TBC disease affected the increase in exacerbation severity (OR=7.25, 95%CI=1.05-50.23, p=0.045), age from smoking >20 years affected the reduction in exacerbation severity (OR=0.03, 95%CI=0.002-0.61, p=0.022). History of alcohol use (OR=7.26 and 167.56, p=0.014 and 0.004) and comorbid pneumonia (OR=28.14 and 44.25, p=0.035 and 0.014) contributed to an increase in the frequency of exacerbations and hospitalization per year. Medium economic status affects the decrease in hospitalizations per year (OR=0.06, 95%CI=0.00-0.91, p=0.043) while the diagnosis of severe COPD and history of alcohol affected the decrease in COPD severity (ABCD) (OR=0.12 and 0.24, p=0.039 and 0.009). **Conclusion:** comorbidities, disease history, history of alcohol use, COPD status and the use of COPD medications contributed to variations therapeutic outcomes COPD patients. Therefore, it must be taken into account when making clinical decisions.

Keywords: COPD; clinical outcomes; factors; therapeutic outcomes

INTRODUCTION

Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines of 2022, Chronic Obstructive Pulmonary Disease (COPD) is a non-communicable disease that is one of the world's health problems. COPD is characterized by persistent respiratory symptoms and limited airflow caused by exposure to harmful particles or gases and affected by the development of abnormal lung function.[1] COPD is marked with distal airways and parenchymal remodeling which can be interpreted as attributable to failed regenerative processes.[2] Despite several years of study on the pathogenesis and therapy of COPD and the discovery and implementation of several effective pharmacological and therapeutic strategies, the medical field has struggled to reduce its morbidity and mortality. This could be due to a variety of variables, including the disease's complexities, which have heterogeneous effects on the airways, pulmonary vasculature, and lung parenchyma, together with the dynamic effects of acute exacerbations.[3]

According to WHO, COPD is the third cause of death for 3.23 million deaths in the world and the fourth cause of death in lower-middle-income countries, 90% of deaths from COPD are 70 years old (recorded until 2019). Based on Indonesia Basic Health Research 2013, the prevalence of COPD reached 3.7% or around 9.2 million people in Indonesia.

Based on a cross-sectional study that analyzed the status of COPD treatment in four Asia Pacific countries, including Indonesia, the clinical characteristics of patients in Indonesia showed the lowest Forced expiratory volume in one second (FEV1) value, the second highest COPD Assessment Test (CAT) value, a highest rates history of exacerbations per year and the highest use of corticosteroid combination inhalation and long-acting agonist β2 (ICS-LABA) which is a therapy for COPD patients with high severity (category D). This shows that COPD patients in Indonesia have a high risk of therapeutic failure.[4]

The effectiveness of COPD therapy is needed to control the pain and mortality rate of COPD patients, so it is important to evaluate the patient's health status.[5] Evaluation is carried out by assessing the clinical outcomes of COPD patients who can determine treatment therapy and determine the success and effectiveness of therapy (Duarte-de-Araújo et al., 2020). Based on GOLD 2022, clinical outcome assessment is carried out by measuring lung function using spirometry, severity

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of shortness of breath using the Modified British Medical Research Council (mMRC) Dyspnea Scale questionnaire, the number of symptoms with CAT, and measuring health status in COPD patients with the St. George's Respiratory Questionnaire (SGRQ) questionnaire. Exacerbation risk must be assessed by knowing the frequency and severity of the patient's exacerbation history. The frequency of exacerbations and hospitalization due to exacerbations is associated with a worsening disease prognosis and an increased risk of death.[1]

Several factors and characteristics of patients affect the clinical outcomes as determinants of the therapeutic success of COPD patients. Several factors contribute to inflammation and fibrosis, including smoking, air pollution, and biomass exposure.[6,7] COPD comorbidities are also linked to worsening symptoms and increased mortality.[6,8] Individual characteristics such as gender, which influence COPD patient therapy, also have a significant impact on therapeutic outcomes.[9] Non-compliance factors and errors of inhaler use are associated with increased CAT values, decreased MMRC values, an increased frequency of exacerbations, and hospitalization.[10] Dosing regimens, comorbidities, age, and economic status of patients are also related to therapeutic outcomes.[11,12]

COPD patients in Indonesia are still high along with the inability to achieve the therapeutic outcomes. This is also supported by limited COPD research in Indonesia. Various factors can affect the therapeutic outcomes that can be assessed through clinical outcomes in such as disease symptoms, risk of exacerbation and patient quality of life. The purpose of this study is to find out which factors affect the outcome of COPD patients to decide the right treatment steps for COPD patients.

METHODS

Study Design and Population

This study was a descriptive-observative study using a cross-sectional design with the subject of COPD patients in outpatient pulmonary polyclinics at RSPAD Gatot Soebroto Jakarta who met the inclusion criteria, including: stable COPD, diagnosed with COPD for at least 1 year, had accessible medical records and agreed with inform consent and complete the questionnaire completely. Exclusion criteria included patients in an acute or exacerbating state, having incomplete and illegible medical records. Gatot Soebroto Army Central Hospital is one of the main tertiary referral hospitals in Indonesia. This research had been approved by the research ethics committee Universitas Padjajaran Bandung with a letter number 788/UN6. KEP/EC/2022 on August 15, 2022.

Source and Types of Primary Data and Secondary Data

The primary data used for the study were the results of patient interviews and questionnaires that had been tested for validity and for reliability with a Cronbach alpha value of ≥0.6. Secondary data comes from patient medical records including patient demographic data, patient medication records, assessment results by pulmonologists, patient clinical data and laboratory test results.

Factor and Characteristics

Factors that influence the success of therapy are determined through the 2022 GOLD guidelines and literature studies from previous research journals. These factors include gender (male or female), age (<40 years, 40-60 years, >60 years), BMI, level of education (<Elementary School, Elementary School, Junior High School, Senior High School, Bachelor / more), occupation (not working, field work/warehousing and office work), work history (not working, field work/warehousing and office work), economic status (low, medium, high, very high), exposure (dust, smoke, air pollution), history of alcohol and drug consumption, smoking status (non-smoker, smoker, ever smoked), age started smoking (<10, 10-15, 16-20 and >20 years), smoking duration (<10, 10-20, >20 years), number of cigarettes/day (<10.10-20,> 20 cigarettes/day), Brinkman Index (Mild, Moderate, Severe), co-morbidities/comorbidities, Charlson Comorbidity Index, history of disease, COPD treatment profile (Regimen compliance with diagnosis, pharmacological regimen, use of xanthine, use of long acting bronchodilators, use of oral steroids, number of drugs, medication adherence (MARS scale) -5 and categories (mild, moderate, severe), correct use of the inhaler (correct and inappropriate), and COPD severity (in the ABCD classification).

Clinical outcomes

Clinical outcomes were determined based on 2022 GOLD guideline and outcomes reported by previous published articles (13,14). The COPD (Chronic Obstructive Pulmonary Disease. Clinical outcomes included physician assessment, mMRC grade (0-5), CAT score, CAT category (<10, 10-19 and >19), exacerbation frequency per year (<2 and ≥2), exacerbation severity (mild, moderate, severe) and hospitalization history per year (0 and >1).

Statistical Analysis

Descriptive analysis was conducted to describe the general characteristics and clinical outcomes of the subjects Correlation analysis was conducted using the Pearson Chi Square and Spearman Rank Test. Independent variables that had a p-value <0.25 were then analyzed by logistic regression test to determine the association and reported as odds ratio. Furthermore, the independent variables that had a p-value <0.5 were analyzed by multivariate logistic regression test to find the factors and characteristics that had the most siginificant effect on clinical outcomes. Data and statistical analysis were performed using Minitab 21.

RESULTS

Patient Characteristics

The demographic data of included 74 outpatient COPD patients Table 1. Most subjects were male patients (95.95%) aged over 60 years (81,1%). Most of the patients lived in Jakarta (77.03%), were married (97.3%) and had high school education (51.35%). Most COPD patients currently do not work or are retirees (72.97%) and have a history of previous work as field and warehouse workers (67.57%) who are exposed to smoke

and dust on a daily basis. The educational backgrounds and economic conditions of COPD patients in this study varied; the majority have very good financial conditions and are recent high school graduates. The patients received varying levels of diagnosis where most were at the COPD Group D level (83.78%).

COPD patients had various exposure history (can be seen in Table 2). The highest is a history of exposure to air pollution (n = 52.7%). Patients with smoking history reached 89.91% and 10.81% of them were still smokers. COPD patients had the highest Brinkman index in terms of weight (n = 60.81%) with a history of starting smoking at most 16-20 years (n = 35.14%), smoking consumption at most > 20 cigarettes/day (n = 54.05%) and smoking duration> 20 years (n = 79.73%). Some patients have a history of drug-induced interstitial lung disease (DIILD) use, alcohol consumption and medication use.

Table 1. Demographic Data of COPD Patients

Characteristic	Total (n=74)	Percentage (%)
Age (mean, SD)	69.42, SD=10.83	
<40 Years	1	1.35
>40 Years	13	17.57
>60 Years	60	81.08
Gender		
Male	71	95.95
Female	3	4.05
Domicile		
Jakarta	57	77.03
Outside Jakarta	17	22.97
Married Status		
Married	72	97.3
Not Married	2	2.7
Last Education		
Elementary School	3	4.05
Junior High School	7	9.46
Senior High School	38	51.35
Higher education	26	35.14
Work		
Retired / Not Working	54	72.97
Field / Warehouse Workers	10	13.51
Office Workers	10	13.51
Prior Employment History		
Not Working	4	5.41
Field / Warehouse Workers	50	67.57
Office Workers	20	27.03
Economic Status		
Very High	33	44.59
High	19	25.68
Moderate	15	20.27
Mild	7	9.46
Body Mass Index (mean,SD)	23.904, SD=4.578	
COPD Diagnosis (Grade)		
Grade A	0	0
Grade B	9	12.16
Grade C	3	4.05
Grade D	62	83.78

Table 2. Data on Exposure, Consumption and Smoking History of COPD Patients

Characteristic	n (=74)	%
Exposure History		
Dust	38	51.35
Air Pollution	39	52.70
Smoke	33	44.59
Alcohol Consumption History	**24**	**32.43**
Drug Consumption History	**4**	**5.41**
Smoking History		
Age Started Smoking (mean, SD)	14.311, SD=7.073	
<10 Years	14	18.92
10-15 Years	25	33.78
16-20 Years	26	35.14
>20 Years	9	12.16
Smoking duration (mean, SD)	33.28, SD=18.47	
< 10 Years	14	18.92
10-20 Years	1	1.35
>20 Years	59	79.73
Cigarettes/Day (mean, SD)	19.68, SD=14.00	
<10 Cigarettes/Day	19	25.68
10-20 Cigarettes/Day	15	20.27
>20 Cigarettes/Day	40	54.05
Brinkman Score (mean, SD)	**755.0, SD= 624,3**	
Brinkman Category		
Mild	20	27.03
Moderate	9	12.16
Heavy	45	60.81
Smoker Status		
Not Smoker	8	10.81
Former Smoker	58	78.38
Smoker	8	10.81
DIILD History	20	27.03

The patients had various history and comorbidities (Table 3). The most common comorbidities suffered by patients were Cardiovascular Disease (CVD) (35.14% and 79.73%, respectively). Charlson Comorbidity Index (CCI) can be used to predict COPD patient mortality. The CCI value in this study averaged 5.378 where a value >3 indicated a higher risk of mortality.[15]

Table 3. Comorbidity Data and Disease History of COPD Patients

Characteristic	Comorbidities		Disease History	
	n	%	n	%
Cancer/Tumor	7	9.46	6	8.11
Type 2 Diabetes	20	27.03	2	2.70
Gastritis	34	45.95	-	-
Asthma	2	2.70	17	22.97
Tuberculosis (TB)	-	-	22	29.73
SOPT	6	8.11	-	-
Covid-19	-	-	23	31.08
Long Covid	2	2.70	-	-
Pneumonia	5	6.76	10	13.51
Lung Mycosis	-	-	3	4.05
Bronchitis	-	-	3	4.05
Bronchiectasis	-	-	1	1.35
Gastritis	34	45.95	-	-
CVD	59	79.73	26	35.14
Psychological Disorder	9	12.16	-	-
Comorbidities (mean, SD)	**1.95, SD= 0.89**			
Charlson Comorbidity Index (mean, SD)	**5.378, SD=1.803**			

*CVD=Cardiovascular Desease

The treatment profile of COPD varied as can be seen in Table 4. Most patients received a complete regimen, including long-acting bronchodilators, short-acting bronchodilators and mucoregulators (n=55.41%), high regimen compliance with a COPD diagnosis (n = 89.19%), and with the number of types of drugs obtained an average of 3-4 drugs (3,622 ± 1,016). Most COPD patients received a prescription for xanthine (n=52.7%). Oral steroids only used in a small proportion of patients (n = 4.05%). ICS/LABA (n = 63.51%) as the Grade D COPD regimen were used in the majority of patients. In this study, the use of mucolytics in the form of mucoregulators was 83.78%. The average patient had medication adherence with a moderate MARS-5 value (72.97%) and most of them were correct in using inhalers (58.11%).

In this study, the clinical outcomes of COPD patients was assessed through an assessment of CAT values, mMRC values, exacerbation frequency, exacerbation severity, history of hospitalization and COPD severity (ABCD level). Assessment using the CAT questionnaire has tested its validity and reliability with a p-value <0.05 and Cronbach alpha >0.6.[13,16,17] As for the mMRC questionnaire, it uses the GOLD 2022 version which has been translated from English to Indonesian using the Back-To-Back Translation Technique with a professional translator. The results of patient assessment after at least 1 year of therapy showed improvement where the CAT score was <10 on average, mMRC value was <2 on average, exacerbation frequency/year <1, hospitalization history/year <1 and COPD patients are currently the most is at grade A which is the mildest level of COPD as stated in the 2022 Global Initiative for Chronic Lung Disease (GOLD).[1,18] Clinical assessment data for patients can be seen in Table 5.

Table 4. Treatment Profile of COPD Patients

Characteristic	n (=74)	%
Regimen Compatibility with COPD Diagnosis	**66**	**89.19**
COPD Regimen		
Long Acting Bronchodilators Only	7	9.46
Long Acting Bronchodilators + Short Acting Bronchodilators	6	8.11
Long Acting Bronchodilators + Mucoregulators	20	27.03
Long Acting Bronchodilators + Short Acting Bronchodilators + Mucoregulators	41	55.41
Number of Drug Types (mean ± SD)	**3.622 ± 1.016**	
Drug Use		
Xanthine	39	52.7
ICS/LABA	47	63.51
Oral Steroid	3	4.05
Ultra Long Acting Bronchodilator	21	28.38
Mucoregulator	62	83.78
Long Acting Bronchodilator Regimen		
LAMA	6	8.11
Xanthine	1	1.35
LAMA + Xanthine	4	5.41
Ultra LABA + Xanthine	2	2.70
Ultra LABA + LAMA	2	2.70
Ultra LABA + LAMA + Xanthine	3	4.05
Ultra LABA/LAMA	2	2.70
Ultra LABA/LAMA + Xanthine	7	9.46
ICS/LABA	5	6.76
ICS/LABA + Xanthine	4	5.41
ICS/LABA + LAMA	15	20.27
ICS/LABA + LAMA + Xanthine	13	17.57
ICS/LABA + LABA + Xanthine	1	1.35
ICS/LABA + Ultra LABA	2	2.70
ICS/LABA + Ultra LABA/LAMA	2	2.70
ICS/LABA + Ultra LABA/LAMA + Xanthine	5	6.76
Short Acting Bronchodilator Regimen		
Without Reliever	27	36.49
SABA	38	51.35
SABA/SAMA	4	5.41
SABA + SABA/SAMA	2	2.70
SABA + Oral Steroid	2	2.70
Oral Steroid	1	1.35

mucoregulator used		
Without Mucoregulator	12	16.22
N-acetylsistein	58	78.38
Ambroxol	4	5.41
Inhaler Type		
pMDI	36	48.65
Soft-mist inhaler	46	62.16
Turbuhaler	25	33.78
Nebulizer	7	9.46
Breezehaler	24	32.43
Discus	22	29.73
Treatment Adherence (MARS-5) (mean ± SD)	22.270 ± 2.711	
Treatment Adherence Category (MARS-5)		
Mild	0	0
Moderate	54	72.97
High	20	27.03
Inhaler Device Use		
Proper	43	58.11
Unproper	31	41.89

Table 5. Data on Clinical Outcomes Assessment Results for COPD Patients

Clinical Outcomes Variables	**n (=74)**	**%**
Exacerbation Frequency/year (mean, SD)	0.3649, SD=0.8371	
0	54	72.97
1	17	22,.7
≥2	3	4.05
Exacerbation Severity		
Mild	53	71.62
Moderate	1	1.35
Heavy	20	2.,03
Hospitalization History/year (mean, SD)	0.2432, SD=0,4626	
0	57	77.03
≥1	17	22.98
CAT Score (mean, SD)	9.784 ± 5.746	
<10	43	58.11
10-19	25	33.78
>19	6	8.11
mMRC Score (mean, SD)	1.257, SD=1.135	
0-1	54	72,97
≥2	20	27,03
Current COPD Grade		
Grade A	29	39.19
Grade B	28	37.84
Grade C	6	8.11
Grade D	11	14.86

Bivariate Analysis Results

Bivariate analysis was applied using the Spearman Rank Test, Chi-Square, and Pearson Chi Square correlation tests and logistic regression, while multivariate analysis was conducted using logistic regression analysis. In this study, the results of the correlation analysis with a p value <0.25 were tested again with the bivariate logistic regression test, to ensure the significance of the association between variables and to equate the model for further multivariate tests. The results can be seen in Table 6. The results of the bivariate logistic regression test with a p value <0.05 were tested on multivariate analysis to determine the most influential factors. The results of the bivariate logistic regression test with a p-value <0.05 can be seen in Table 7.

The mMRC score is an assessment of the degree of shortness of breath that is considered to assess symptoms of shortness of breath, health status and predict mortality.[19] In this study, the history of alcohol consumption in COPD patients significantly associated with the mMRC value. Type 2 Diabetes Mellitus (DM) dan use of xanthin also associated with poorer mMRC score.

In the bivariate test results, moderate economic status, history of air pollution exposure and history of tuberculosis disease had a significant effect with an odds ratio that decreased the frequency of exacerbations per year. On the other hand, history of alcohol consumption, comorbid pneumonia and ICS/LABA use had a significant effect on the odds ratio of worsening the frequency of exacerbations per year.

Based on the results of bivariate tests, low CAT scores were significantly associated with history of alcohol consumption, Brinkman scores both moderate and severe, tumor/cancer comorbidities and number of types of drugs. Meanwhile, a history useful for assessing the number of symptoms that COPD patients present with as an evaluation of improvement and worsening of therapy outcomes.[19]

Severity of exacerbations was significantly associated with moderate and high economic status, history of air pollution and history of tuberculosis with an odds ratio of worsening exacerbations in COPD patients. Meanwhile, history of alcohol consumption, smoking age >20 years and comorbid pneumonia had a significant effect in reducing the severity of exacerbations of COPD patients.

Moderate economic status and a history of air pollution exposure are associated with reduce hospitalization per year. Whereas a history of alcohol consumption, comorbid pneumonia and the use of ICS/LABA significantly increase hospitalization per year.

COPD patients with junior and senior high school education had a significant association with increasing COPD severity (Grade ABCD). On the other hand, previous COPD diagnosis, history of alcohol consumption, smoking age 10-15 years

Table 6. Correlation Test Results with p-value <0.25 and <0.05

Characteristic	CAT	mMRC	Exacerbation Frequency	Exacerbation Severity	Hospitalization History	Current Grade ABCD
	p-value					
Age	*>0.250*	*>0.250*	**0.154**	*>0.250*	*>0.250*	*>0.250*
Last Education	*>0.250*	*>0.250*	0.134	0.067	0.114	0.075
Work	0.059	0.205	*>0.250*	0.231	*>0.250*	*>0.250*
Prior Employment History	*>0.250*	0.181	*>0.250*	0.208	0.229	0.059
Economic Status	*>0.250*	*>0.250*	0.117	0.067	0.079	*>0.250*
Body Mass Index (BMI)	*>0.250*	*>0.250*	0.231	*>0.250*	*>0.250*	*>0.250*
COPD Diagnosis (Grade)	**0.043**	*>0.250*	**0.022**	0.105	**0.04**	**0.003**
Exposure History						
Dust	*>0.250*	0.234	*>0.250*	*>0.250*	*>0.250*	*>0.250*
Air Pollution	*>0.250*	*>0.250*	**0.017**	**0.047**	**0.028**	*>0.250*
Smoke	*>0.250*	*>0.250*	*>0.250*	*>0.250*	*>0.250*	*>0.250*
Alcohol Consumption History	**0.047**	**0.049**	**0.012**	**0.015**	**0.008**	**0.005**
Drug History	>0.250	0.211	0.211	0.205	>0.250	>0.250
Smoking History						
Age Started Smoking	*>0.250*	0.14	0.287	**0.016**	0.067	*>0.250*
Long Smoking	**0.013**	*>0.250*	0.178	**0.04**	*>0.250*	**0.004**
Sticks/day	0.075	*>0.250*	0.075	0.067	*>0.250*	**0.005**
Brinkman Score	0.157	*>0.250*	0.122	*>0.250*	*>0.250*	*>0.250*
Brinkman Category	**0.036**	*>0.250*	0.145	0.135	*>0.250*	**0.009**
DIILD History	*>0.250*	*>0.250*	0.126	*>0.250*	0.134	0.146
Comorbidities						
Cancer/Tumor	0.014	*>0.250*	*>0.250*	*>0.250*	*>0.250*	*>0.250*
Type 2 Diabetes	*>0.250*	**0.034**	*>0.250*	*>0.250*	*>0.250*	*>0.250*
Gastritis	0.192	0.057	*>0.250*	*>0.250*	0.51	*>0.250*
Asthma	0.172	*>0.250*	*>0.250*	*>0.250*	*>0.250*	0.164
SOPT	*>0.250*	*>0.250*	0.12	0.114	0.163	*>0.250*
Long Covid	*>0.250*	*>0.250*	*>0.250*	*>0.250*	*>0.250*	0.176
Pneumonia	*>0.250*	*>0.250*	**0.006**	**0.006**	**0.002**	0.174
CVD	0.029	0.129	*>0.250*	0.235	*>0.250*	0.156
Charlson Comorbidity Index	0.243	>0.250	0.202	0.163	0.135	*>0.250*
Disease History						
Type 2 Diabetes	0.1721	*>0.250*	*>0.250*	*>0.250*	*>0.250*	0.164
Tuberculosis (TBC)	0.253	*>0.250*	0.024	**0.019**	0.214	*>0.250*
Covid-19	*>0.250*	0.046	*>0.250*	*>0.250*	*>0.250*	*>0.250*
Pneumonia	*>0.250*	*>0.250*	*>0.250*	0.089	0.57	*>0.250*
Lung Mycosis	0.133	*>0.250*	*>0.250*	*>0.250*	*>0.250*	0.093
Bronchitis	0.133	0.176	0.176	0.124	0.13	*>0.250*
CVD	*>0.250*	*>0.250*	0.141	0.0807	0.085	*>0.250*

Regimen Compatibility with COPD diagnosis	**0.011**	*>0.250*	0.068	0.063	0.102	*>0.250*
Pharmacological Regimen	0.234	0.151	*>0.250*	*>0.250*	*>0.250*	0.098
Number of Drug Types	**0.015**	**0.033**	**0.026**	0.162	0.142	**0.003**
Drug Use						
Xanthine	**0.034**	**0.019**	0.197	*>0.250*	*>0.250*	0.078
Oral Steroid	0.133	0.1758	*>0.250*	*>0.250*	*>0.250*	*>0.250*
ICS/LABA	*>0.250*	0.177	*>0.250*	*>0.250*	*>0.250*	*>0.250*
Ultra Long Acting Bronchodilator	*>0.250*	0.084	*>0.250*	*>0.250*	0.149	*>0.250*
Mucoregulator	*>0.250*	*>0.250*	0.236	*>0.250*	*>0.250*	*>0.250*
Treatment Adherence (MARS-5)	*>0.250*	*>0.250*	0.156	0.13	*>0.250*	*>0.250*
Inhaler Device Use	0.055	*>0.250*	*>0.250*	*>0.250*	*>0.250*	*>0.250*

* p-value <0,05 bolded.

Table 7. Logistic Regression Bivariate Test Results with p-value <0.05

Characteristics_Reference	**Odd Ratio**	**95% CI**		**p-value**
		Lower	**Upper**	
CAT Score				
Alcohol Consumption History	2.72	1.00	7.39	0.05
Brinkman Score	1.00	1.00	1.00	0.018
Brinkman Category_Mild				
Moderate	8.00	1.37	46.81	0.021
Heavy	3.50	1.01	12.12	0.048
Cancer/Tumor Comorbid	10.08	1.15	88.65	0.037
CVD Comorbid	0.28	0.80	0.92	0.035
Number of Drug Types	1.80	1.06	3.07	0.031
mMRC Score				
Alcohol Consumption History	2.86	0.98	8.31	0.054
Type 2 Diabetes Comorbidity	3.20	1.06	9.63	0.039
Use of Xanthine	3.75	1.19	11.79	0.024
Use of ICS/LABA	0.26	0.09	0.75	0.013
Exacerbation Frequency/year				
Economic Status_Low				
Moderate	0.18	0.04	0.92	0.039
History of Air Pollution Exposure	0.27	0.09	0.82	0.021
Alcohol Consumption History	3.85	1.31	11.34	0.014
Pneumonia Comorbid	13.25	1.38	127.17	0.025
History of TB disease	0.19	0.04	0.90	0.036
Use of ICS/LABA	4.53	1.19	17.31	0.027
Exacerbation Severity				
Economic Status_Low				
Moderate	3.81	0.93	15.54	0.063
High	10.06	1.19	85.35	0.034
History of Air Pollution Exposure	2.95	1.03	8.50	0.045
Alcohol Consumption History	0.28	0.10	0.81	0.019

Age Start Smoking_<10 years				
>20 years	0.06	0.00	0.65	0.021
Pneumonia Comorbid	0.08	0.01	0.73	0.025
TBC Disease History	5.70	1.20	26.98	0.028
Hospitalization History/year				
Economic Status_Low				
Moderate	0.10	0.01	0.82	0.032
History of Air Pollution Exposure	0.28	0.09	0.91	0.034
Alcohol Consumption History	4.39	1.41	13.70	0.011
Pneumonia Comorbid	17.23	1.78	167.26	0.014
Use of ICS/LABA	5.86	1.22	28.04	0.027
Current COPD Severity (ABCD Grade)				
Last Education_Elementary School				
Junior High School	15.61	1.11	218.50	0.041
Senior High School	12.11	1.23	119.21	0.033
COPD Dignosis_Grade B				
Grade D	0.12	0.02	0.66	0.015
History of Alcohol Consumption	0.18	0.07	0.48	0.001
Age Start Smoking_<10 years				
10-15 years	0.09	0.02	0.38	0.001
16-20 years	0.14	0.03	0.60	0.008
Smoking duration_<10 years				
>20 years	0.14	0.04	0.53	0.004
Brinkman Category				
Moderate	0.21	0.04	0.97	0.046
Heavy	0.17	0.06	0.53	0.002
Number of Drug Types	0.55	0.35	0.87	0.010
Use of Xanthine Drugs	0.32	0.13	0.77	0.011

and 16-20 years, smoking duration >20 years, moderate and severe Brinkman score, number of medications and xanthine medication may significantly reduce the COPD severity (Grade ABCD).

Prescribed pharmacological therapy requires patient's adherence and correctness of use to achieve the optimal outcomes. This study also assessed patient treatment adherence using the MARS-5 questionnaire which had been tested for validity and reliability with a p-value <0.05 and Cronbach alpha >0.6 (0.7485).

The accuracy of inhaler use is assessed using the Device Specific Checklist Inhaler Technique, National Asthma Council, Australia by adjusting the inhaler items available in Indonesia. In this study, medication adherence and the accuracy of inhaler use did not show a significant correlation with the value of successful therapy for COPD patients. This is because there was not a single patient with low medication adherence and most of them had used the inhaler properly. The most common inhaler use errors are listed in Table 8.

Multivariate Analysis Results

In the multivariate test results listed in Table 9, the presence of tumor/cancer comorbidity was the most significant factor associated with the increase of CAT value. ICS/LABA use was the most significant factor associated with improvement in mMRC value. History of alcohol consumption and comorbid pneumonia were the most significant factors associated with the increase of exacerbations frequency. History of tuberculosis disease and age of start smoking >20 years had the strongest influence on exacerbation severity, in which age of start smoking >20 years had a probability of reducing exacerbation severity while history of tuberculosis had a higher probability of COPD exacerbations. Moderate economic status had a significant association with the increase of hospitalization per year, while a history of alcohol consumption and comorbid pneumonia had the most significant effect in increasing the hospitalization of COPD patients per year. A diagnosis of COPD with grade D severity and a history of alcohol consumption had the strongest associations in reducing COPD severity (Grade ABCD).

Table 8. The Most Common Errors of Using Inhalers in COPD Patients			
Inhaler Use Stage		**N**	**%**
pMDI (n=36)			
1.	Hold the inhaler upright and shake it up and down	10	27.78
2.	Exhale maximally slowly	7	19.44
3.	Inhale slowly and deeply through the mouth and at the same time press firmly on the tube	4	11.11
4.	Hold breath for about 5 seconds	8	22.22
5.	Exhale gently, away from the inhaler	7	19.44
Turbuhaler (n=25)			
1.	Exhale maximally slowly, away from the inhaler	5	20
2.	Hold breath for about 5 seconds	5	20
3.	Exhale gently, away from the inhaler	5	20
Soft-mist inhaler (n=46)			
1.	Exhale maximally slowly, away from the inhaler	6	13.04
2.	Hold breath for about 5 seconds	6	13.04
3.	Exhale gently, away from the inhaler	5	10.87
Breezehaler (n=24)			
1.	Exhale maximally slowly, away from the inhaler	10	41.67
2.	Take deep, steady breaths until the capsule vibrates	3	12.50
3.	Hold breath for about 5 seconds	6	25
4.	While holding your breath, remove the inhaler from your mouth	3	12.50
5.	Exhale gently, away from the inhaler	4	16.67
Discus (n=22)			
1.	Exhale maximally slowly, away from the inhaler	5	22.73
2.	Hold breath for about 5 seconds	6	27.27
3.	While holding your breath, remove the inhaler from your mouth	5	22.73
4.	Exhale gently, away from the inhaler	5	22.73

Table 9. Multivariate Test Results				
Characteristic_Reference	**Odds Ratio**	**95% CI**		**p-value**
		Lower	**Upper**	
CAT Score				
Alcohol Consumption History	0.38	0.11	1.27	0.115
Brinkman Category_Low				
Moderate	4.01	0.53	30.29	0.179
Heavy	0.37	0.04	3.57	0.386
Tumors/Cancer Comorbid	**10.90**	**1.01**	**117.23**	**0.049**
CVD Comorbid	0.28	0.06	1.34	0.112
Number of Drug Types	1.72	0.88	3.37	0.113
mMRC Score				
Alcohol Consumption History	2.73	0.81	9.19	0.104
Type 2 Diabetes Comorbidity	3.45	0.99	11.96	0.051
Use of Xanthine	3.45	0.97	12.28	0.056
Use of ICS/LABA	**0.26**	**0.08**	**0.84**	**0.024**
Exacerbation Frequency				
Economic Status_Low				
Moderate	0.23	0.03	1.90	0.174
High	0.18	0.02	1.45	0.107
Very High	0.45	0.05	4.37	0.488
Pollution Exposure History	0.32	0.07	1.41	0.131
Alcohol Consumption History	**7.26**	**1.50**	**35.04**	**0.014**
Pneumonia Comorbidity	**28.14**	**1.26**	**625.95**	**0.035**
TB history	0.37	0.06	2.28	0.284
Use of ICS/LABA	4.20	0.75	23.51	0.102

Exacerbation Severity				
Economic Status_Low				
Moderate	2.9	0.42	20.09	0.280
High	9.41	0.78	113.34	0.078
Very High	3.58	0.31	41.41	0.307
Pollution Exposure History	2.44	0.53	11.27	0.252
Alcohol History	0.2	0.04	1.05	0.057
Age Started Smoking_<10 years				
10-15 years	0.23	0.01	3.56	0.294
16-20 years	0.23	0.02	3.18	0.272
>20 years	**0.03**	**0.002**	**0.61**	**0.022**
Pneumonia Comorbidity	0.01	0.0001	2.04	0.090
TB History	**7.25**	**1.05**	**50.23**	**0.045**
Hospitalization history/years				
Economic Status				
Moderate	**0,06**	**0,00**	**0,91**	**0,043**
High	0,12	0,01	1,27	0,078
Very High	0,15	0,01	2,34	0,176
Pollution Exposure History	0,32	0,06	1,73	0,185
Alcohol History	**17,56**	**2,48**	**124,29**	**0,004**
Pneumonia Comorbidity	**44,25**	**2,16**	**905,27**	**0,014**
Use of ICS/LABA	7,08	0,88	57,25	0,066
Current COPD Severity (Grade ABCD)				
Employment history_retired				
Field/Warehousing Workers	0.27	0.01	6.04	0.409
Office Workers	0.29	0.01	6.63	0.441
COPD Diagnosis				
Grade C	0.17	0.01	5.9	0.329
Grade D	**0.12**	**0.01**	**0.89**	**0.039**
Alcohol Consumption History	**0.24**	**0.08**	**0.71**	**0.009**
Age Started Smoking				
10-15 years	0.23	0.03	1.99	0.184
16-20 years	0.31	0.04	2.26	0.246
>20 years	0.23	0.02	3.03	0.264
Brinkman Category				
Moderate	0.5	0.06	4.5	0.539
Heavy	0.61	0.06	5.97	0.675
Number of Drug Types	0.93	0.5	1.74	0.822
Use of Xanthine	0.46	0.14	1.47	0.19

* significantly associated factors are bolded (p-value<0.05).

DISCUSSION

In this study, the majority of COPD patients were male with an elderly age which is related to the prevalence of smoking in Indonesia which is dominated by men and the progressive reduction in lung organ function resulting expansion of the alveolar cavity and reduced lung elasticity.[9,20] The majority of COPD patients have history of previous work as field and warehouse workers who are exposed to smoke and dust on a daily associated with airflow limitation, respiratory distress symptoms, presence of emphysema and gas trapping in the lungs.[21]

Most of subjects have a fairly high level of economy and education that is associated with an increased risk of COPD events which is related to differences in environment and residential density, nutritional differences, and other factors such as different treatment standards.[22] The majority of the subjects had an initial diagnosis of COPD at high level (Grade D) that in line with the findings from previous study by Choi et al. (2022), which found that COPD patients in Indonesia have the lowest CAT scores and a high frequency of exacerbations compared to other Asian countries, which are associated with various exposure histories. Patients with smoking histories reached 89.91%, 10.81% of them were still smokers that matched with the study by Choi et al., 2022, which showed 84% of Indonesian respondents had a history of smoking. COPD patients in this study had the highest Brinkman index (n = 60.81%), and similar to previous studies in Indonesia, heavy smokers have the highest rates in COPD patients.[23]

The subjects had various histories and comorbidities. The most common comorbidities suffered by patients were cardiovascular diseases (CVD). This is in line with previous research that found the congestive heart failure (CHF), hypertension-related heart disease (HHD), coronary artery disease (CAD), and hypertension are the most common comorbidities in COPD patients in two hospitals.[24,25] Charlson Comorbidity Index (CCI) values can be used to predict COPD patient mortality. The CCI value in this study averaged 5.378, where a value >3 indicated a higher risk of mortality.[21] The CCI value in this study shows that the average survival of COPD patients to 10 years is around 21%.[26]

The treatment profile of the subjects varied, as can be seen in Table 4. Most COPD patients received a prescription for xanthine. The use of xanthine requires attention because of its therapeutic effectiveness, which is still controversial.[27] One study in Indonesia stated that the use of low doses of theophylline can reduce CAT values, increase FEV1 values, and reduce symptoms of shortness of breath when used together with salmeterol. However, its effectiveness against exacerbations in severe COPD is insignificant.[28,29]

Oral steroids are only used in a small proportion of patients; this is related to long-term use, which causes many side effects compared to the benefits. Interesting results was found with regards to the use of ICS and LABA. ICS/LABA is a Grade D COPD regimen with various considerations, such as history of hospitalization and frequency of exacerbations, eosinophil levels 300 cells/l, and history and comorbidity of asthma.

However, the use of ICS/LABA in this study was considered high due to the absence of such assessment, thus it is interesting to test its effect. In this study, the use of mucolytics in the form of mucoregulators was 83.78%. The use of mucolytics such as N-acetylcysteine can reduce exacerbations and improve health status.[30]

In this study, the average patient had medication adherence with a moderate MARS-5 value, and most of them were correctly administering the inhalers. This is in accordance with previous studies where most COPD patients' adherence was 'not fixed or changing' with the Morisky Modified Scale (MMS) questionnaire. The accuracy of using inhalers is related to the success of therapy; a recent study in Indonesia showed an effect on FEV1 values.[15]

In the bivariate test, frequency of exacerbation and history of hospitalization have a significant effect with economic status, where the higher the economic status, the lower the patient's exacerbation frequency. In previous studies, the results of longitudinal analysis showed that low economic status was associated with an increased risk of acute exacerbations (HR 2.1; 95% CI 1.4 to 3.4) and the risk of hospitalization. In this study, the level of education had a significant relationship with the severity of COPD, which is related to poor health status as in the study by Eisner et al., 2011. Based on previous studies, low educational level and economic status are associated with disease severity, worsening lung function, and physical function limitations.[31]

Interestingly, air pollution exposure has a significant negative correlation with the frequency of exacerbations and history of hospitalization. This is because the COPD patient population in Indonesia has a higher population exposed to air pollution due to the relative increase in the use of motorcycles, burning garbage, and others.[32] In addition, in this study, the intensity or severity of exposure to air pollution in COPD patients was unknown. Air pollution contains toxic particles and gases produced from combustible materials, including particulate matter and ozone, as well as biological contaminants such as viruses and bacteria that can penetrate the human airway and reach the bloodstream, triggering airway inflammation, lung dysfunction, and fibrosis. COPD patients often experience exacerbations and worsening of symptoms due to air pollution.[33] This is similar to the results of the exacerbation severity variable bivariate test, where air pollution increases the severity of exacerbations in COPD patients in this study.

Based on bivariate analysis, CAT values were significantly influenced by history of alcohol consumption, as in previous research, which stated that duration of alcohol consumption had an effect on chronic cough (OR = 2.7,p = 0.003) and chronic phlegm (OR = 3.06, p = 0.002), which were Questions 1 and 2 on the CAT, which had the highest average score (P1 = 2.27 and P2 = 2.28.[34] Long-term use of heavy alcohol is known to impair mucociliary clearance, complicate the treatment of asthma and COPD, worsen lung function, and increase mortality in COPD patients.[35]

The mMRC variable is an assessment of the degree of shortness of breath that is considered to assess symptoms of shortness of breath, health status, and predict mortality.[19] In this study, the history of alcohol consumption in COPD patients almost significantly affected the mMRC value. The history of alcohol consumption has a significant effect on the frequency of exacerbations and the history of hospitalization. Previous studies have shown that alcohol consumption has an effect on decreasing FEV1 values on spirometry and has an independent additive negative effect on lung function (Frantz et al., 2014) related to the onset of shortness of breath symptoms.[34]

In this study, a history of alcohol use was associated with a decrease in exacerbation severity and COPD severity scores (ABCD). This is consistent with recent research, which shows that drinking alcohol, such as wine or beer, lowers the risk of COPD (p = 0.001).[35] In this study, the frequency of alcohol use and the type of alcohol used were not known, causing the odds ratio to be reversed. As in previous studies, this study also has limitations in that patient assessment was carried out without measuring FEV1 by spirometry (Kaluza et al., 2019) and cannot exclude the possibility of misdiagnosis of COPD with heart failure, which can result in an inverse relationship between alcohol and COPD.[19,36]

The Brinkman index is a calculation of the severity of smoking by multiplying the average number of cigarettes smoked per day by the length of time smoked in years.[37] The results of the bivariate test with the correlation and logistic regression tests showed that the Brinkman index had a significant effect on CAT values in both heavy and moderate smokers. This is related to previous studies where, in the working population, the smoking index (pack-years) was significantly related to CAT scores, both mild (OR = 1.8; p = 0.04) and heavy (OR = 1.9; p = 0.02).[36] A history of smoking results in symptoms of chronic cough, small airway obstruction, and airflow obstruction.[7,38] Meanwhile, quitting smoking can slow down the decline in lung function and reduce mortality and morbidity, even when patients diagnosed with severe COPD are compared to those who are still smoking.[33,34] In this study, the age at which a person started smoking (>20 years old) had an effect on the severity of exacerbations and the severity of current COPD, where the older you start smoking, the lighter the exacerbations and the severity of COPD. This is similar to previous research, where people who start smoking before the age of 18 are more at risk of experiencing airway obstruction.[35]

Comorbidities can exacerbate the clinical symptoms of COPD and vice versa.[1] In this study, COPD patients with cancer/tumor comorbidities and Cardiovascular Disease (CVD) had a significant effect from the results of the bivariate test on CAT scores, as was the case in the Chubachi et al. study with p = 0.0042 in cancer/tumor comorbidities and p = 0.0012 in comorbid CVD. In this study, patients with comorbid CVD had no association to the outcome, which was contrary to Chubachi et al. where patients with comorbid CVD had a lower average CAT score than without comorbid CVD. In previous research by Cheng et al., 2019, it was shown that CVD has no significant effect on CAT values. This is influenced by differences in patient populations and regions, where CVD comorbidities in COPD

patients in Indonesia have a higher frequency according to the proportion of the COPD population with CVD in this study.[24,25]

The results of the bivariate test for type 2 diabetes mellitus (DM) have a significant relationship to the value of mMRC as a clinical outcome. In previous studies, diabetes mellitus comorbidity had a significant relationship to mMRC values (p = 0.014) and mortality (HR = 1.7; p = 0.06), where COPD patients with diabetes mellitus had the worst survival rate among other comorbidities.[39,40] DM comorbidity had a significant effect (p = 0.023) on mMRC values, with higher mMRC values than other comorbidities.[40] COPD patients with diabetes mellitus experience an increase in the plasma systemic inflammatory marker C-reactive protein, which is an independent predictor that greatly influences hospitalization and mortality of COPD patients, affects poor quality of life and lung function, and is related to platelet dysfunction and modification, which causes systemic inflammation, so it is necessary to pay attention to the use of DM and COPD drugs in patients according to their respective treatment guidelines.[1,41-43]

COPD patients with pneumonia have a higher risk of exacerbation and higher hospitalization rates. This is in line with previous studies that found that COPD patients with pneumonia experienced more exacerbations for the first time and were difficult to treat until the seventh or more exacerbations, so COPD patients with pneumonia had a high risk of exacerbations and hospitalizations, which could increase mortality. This is related to the phenotype associated with increased airway inflammation.[44]

A history of tuberculosis (TB) is a risk factor for COPD, and the prevalence of COPD patients with a history of previous tuberculosis is 21%.[45] Studies comparing the history of TB with its severity, as well as clinical outcomes and aggravating factors for COPD, are scarce. Previous research also showed that COPD patients with a history of tuberculosis increased the risk of hospitalization, reduced respiratory function through FEV1 assessment, and increased mortality 5 times worse.[46] Tuberculosis can cause lung parenchymal remodeling, including cavitation, fibrosis, bronchiectasis, and lung damage, which are important factors in the development of COPD. Impaired cellular immunity in COPD patients can become more serious in patients with tuberculosis. However, the effect of TB on COPD severity and clinical outcomes has not been studied.[44-47]

In this study, patients with a history of TB had an increased risk of exacerbation severity and decreased exacerbation frequency. This allows for the effect that COPD patients with a history of tuberculosis are at risk of exacerbations that are rare or perhaps occasional but with a high degree of severity. As stated by Park et al. (2018) in their research, the effect of a history of tuberculosis on the clinical outcomes of COPD needs further investigation.[44] The therapeutic effect of methylxanthine is still in controversy. Several studies state that xanthine works by inhibiting phosphodiesterase as a bronchodilator, but other studies also state that xanthine does not have a bronchodilator action.[48] In this study, the use of xanthine increased the mMRC value, so that the success of COPD therapy was lower than therapy without the use of xanthine. Recent meta-analysis research shows that the addition of theophylline therapy to ICS therapy in COPD patients has a higher risk of exacerbations and hospitalization than the placebo group.[27] In a recent study, the use of methylxanthine with both theophylline and doxophylline and acebrophylline in addition to COPD therapy showed an improvement up to day 42, but not significantly. This is in line with this study, where the use of methylxanthine in COPD therapy improved the outcomes.[28] The higher the mMRC, the worse the shortness of breath. Factors associated with consistent use of xanthine drugs significantly affect mMRC values. In other outcomes that did not show significance (p 0.25 in the bivariate logistic regression test), the use of xanthine had an OR> 1 on CAT scores and exacerbations. It is a concern that the use of xanthine in COPD therapy should be avoided due to its controversial effectiveness and considering its toxicity.[29] The dose-related toxicity of xanthine derivatives is a matter of concern because the therapeutic index is narrow and most of the benefits can only be obtained at doses close to toxic. The most detrimental toxicity is palpitations due to atrial and ventricular arrhythmias, which can be fatal and cause grand mal seizures in patients even without a history of previous epilepsy.[18, 49-52]

The use of ICS and LABA significantly reduced mMRC values. As in previous studies, the combination of ICS and LABA compared to each drug is effective in improving lung function and health status and reducing exacerbations.[53,54] However, clinical trials with survival outcomes were not significant.[51] In RCT studies, it was shown that the ICS/LABA combination reduced the frequency of exacerbations but did not significantly affect CAT values. This is consistent with this study, which found that the use of ICS or LABA has no significant effect on CAT scores.[55] In the variable frequency of exacerbations and history of hospitalization, there was an increase in the use of ICS and LABA. This was caused by the use of ICS/LABA in most of the study subjects without an assessment of blood eosinophil examination, exacerbation and hospitalization histories, or a history of asthma, resulting in biased results in the use of ICS/LABA on variable exacerbation frequency and hospitalization history.[56]

The number of drugs has a significant relationship, namely increasing CAT and mMRC values in bivariate test results. This shows that adding more drugs can result in more severe COPD conditions in CAT and mMRC. In this condition, unavoidable selection bias can occur, such as the influence of the patient's previous condition, which does affect the severity of the CAT and mMRC value.[57]

Bivariate test results on the assessment of COPD severity (ABCD) with the number of types of drugs and use of xanthine have a negative correlation. Where the use of more types of drugs affects the reduction in COPD severity (ABCD), so does the use of xanthine. This is in contrast to the mMRC and CAT variables. The results of the bivariate test showed that an increase in the number of types of drugs and the use of xanthine did not significantly affect the frequency of exacerbations or the history of hospitalization, while the COPD severity assessment (ABCD) involved both of these, so the results showed a

negative correlation. However, from existing research, xanthine has a higher risk of exacerbation and hospitalization than the placebo group.[27]

Cancer/tumor comorbidity has the strongest association with CAT scores. In previous studies, malignant comorbidity had a significant effect on CAT scores (p=0.0042).[58] In this study, 4 COPD patients had lung cancer, and 3 others had extrapulmonary cancer. Genetic susceptibility, epigenetic changes in DNA methylation, chronic inflammation of the lung, and abnormal lung repair are important contributors to disease development in lung cancer patients with COPD, which are associated with increased CAT scores.[59] Tumor and cancer comorbidity factors have consistent results in all tests of CAT values, so they need to be considered. An important preventive measure to improve patient survival is to avoid or quit smoking in smoking patients. Quitting smoking provides a temporary improvement in FEV1 and minimizes permanent damage to the lungs. In addition, low-dose chest computed tomography (LDCT) is recommended for lung cancer screening in COPD patients due to smoking.[1] In the mMRC score, multivariate test results showed that the use of ICS or LABA was the most influential factor. The use of ICS or LABA has a consistent effect on all tests, so its use can be considered. However, its use must still be based on assessment (blood eosinophils, history of asthma, and history of exacerbations), because in this study the use of ICS/LABA did not significantly affect the frequency of exacerbations and history of hospitalization in a multivariate analysis. The blood eosinophil count assists clinicians in estimating the possibility of a beneficial preventive response in the patient's body with the use of ICS/LABA.[60] Therefore, the decision to use ICS or LABA should be based on the blood eosinophil count together with an assessment of the history of asthma and exacerbations.

The frequency of exacerbations and history of hospitalization were most influenced by a history of alcohol use and comorbid pneumonia. Matters relating to the results of this study have been explained in the results of the bivariate test. Alcohol consumption has a consistent significance in the results of bivariate and multivariate tests related to exacerbations, so the impact of alcohol consumption on the success of therapy needs to be considered both in terms of intensity and level. Low alcohol consumption at low intensity may be tolerated and provide protection for lung function, as in the study of Kaluza et al., 2019, but the use of alcohol at high intensity and high levels needs to be avoided and further investigated.[35,61]

In the exacerbation severity outcome, the results of the multivariate test showed that the age at which a person started smoking (>20 years) and a history of tuberculosis were the most influential factors on the severity of exacerbations. COPD patients with a history of smoking who started smoking at an older age (>20 years) experienced fewer severe exacerbations than those who started smoking at a younger age (10 years). The history of TB disease has consistently significant results on the severity of exacerbations in both bivariate and multivariate tests, so research on COPD patients with a history of TB needs to be considered. As stated by Park et al. (2018), research on the effect of TB history on COPD clinical outcomes needs to be carried out further due to lack of studies related to TB history and COPD clinical outcomes.[44, 47] The COPD severity score (ABCD) was strongly influenced by the diagnosis of COPD severity and history of alcohol use, with results that were in contrast to other treatment outcomes. The interesting findings of this study is that association between investigated factors and therapeutic outcomes do not always consistent among different outcome definitions. Therefore, it is important to choose a representative outcome that is relevant with patient's condition.

This study possess several strength. We applied various clinical outcomes that are in accordance with the GOLD guidelines and represent the quality of life of patients in terms of COPD symptoms, breathlessness, and exacerbations. Moreover, the measuring instrument used has been tested for validity and reliability so that it can be applied in further research. However, we also acknowledge the study limitations. Due to COVID-19, clinical outcomes in the form of lung function as measured by spirometry could not be obtained. The results of lung function measurements are an important outcome in assessing the success of therapy.[1] In future studies, FEV1 measurement as a measure of lung function is needed as a clinical outcome that determines the success of therapy. In addition, the study population is rather small. Further multicenter research is recommended to obtain a larger number of subjects so that associated factors and therapeutic outcomes that have contradictory results are able to be studied further. In addition, data collection was carried out in a cross-sectional manner and did not repeatedly measured. It was possible that patients were not in actual conditions despite the treatment adherence and the accuracy of inhaler use in the majority of patients in this study had a high result.

CONCLUSION

Clinical outcomes in COPD patients were influenced by comorbidities, disease history, history of alcohol use, COPD status and the use of COPD drugs. These factors need to be considered in the decision of therapy selection or therapy addition.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Universitas Padjajaran Bandung with a letter number 788/UN6.KEP/EC/2022 on August 15, 2022.

DISCLOSURE

The author reports no conflicts of interest in this work.

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