Original Article

Association Between the Severity of Chronic Obstructive Pulmonary Disease and the Probability of Pulmonary Hypertension In a Tertiary Hospital

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) patients with pulmonary hypertension (PH) have a poor prognosis, which worries doctors. The prevalence of COPD-related PH is unclear. The lack of anatomical criteria for right ventricular hypertrophy may explain research variance. Only type 1 PH patients undergo direct right cardiac catheterization of pulmonary artery pressure.

Methods: A cross-sectional analytical descriptive study examined stable COPD patients visiting the pulmonary department at M. Djamil Hospital, Padang, from November 2023 to February 2024 for PH probability.

Results: This study included 64 participants, with a majority aged between 40 and 65 years (59.4%), a significant proportion male (82.8%), and a junior high school (29.7%) level of education. Most of the subjects smoked (81.2%), had severe Brinkman Index (75.0%), had severe GOLD criteria (50.0%), and had no comorbidities (53.1%). No correlation was found between the severity of COPD and the likelihood of PH (*P*=0.591). The Brinkman Index of smokers was a significant risk factor for PH (*P*=0.010; OR=1.282; 95% CI=0.260-6.315).

Conclusion: There is no significant association between the severity of COPD according to GOLD criteria and the likelihood of PH.

Keywords: Brinkman index, COPD, pulmonary hypertension

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INTRODUCTION

Not all stable chronic obstructive pulmonary disease (COPD) patients will develop pulmonary hypertension (PH). There are no specific guidelines or criteria for which stable COPD conditions are at risk of developing pulmonary hypertension. COPD patients with PH will get additional advanced treatment therapy, different from that of patients without PH. This study aimed to assess the association between the severity of COPD and the incidence of pulmonary hypertension.

Pulmonary hypertension can develop as a side effect of some treatments or as a standalone illness with no known etiology (idiopathic pulmonary arterial hypertension). There are currently five primary ways that PH is classified, including processes with similar pathogenic origins. Hypoxia or pulmonary illness are two causes of PH that fall into the third category. COPD is the most prevalent form of PH.[1]

The prevalence of PH in COPD is unknown, as there is no systematic and commonly utilized screening method.[1] Anatomical evidence of right ventricular hypertrophy in people with COPD is observed at autopsy in up to 40% of cases. The variation in research may stem from the absence of standardized morphological criteria for defining right ventricular hypertrophy.[2]

Direct measurement of pulmonary artery pressure (Ppa) via right cardiac catheterization is conducted in a limited cohort of individuals. A 2021 study by Agus at Arifin Achmad Hospital indicated that 51.7% of COPD patients with a Forced Expiratory Volume in the first second (FEV_1) score <50% exhibited pulmonary hypertension.[2]

The predominant cardiac pathological finding is right ventricular hypertrophy, observed in 64.8% of cases. Left ventricular diastolic function is compromised at 52.3%, while tricuspid regurgitation is present at 35.2%. The abnormal signs observed

on echocardiography are more common in the GOLD III and IV groups. There is a significant correlation between the severity of COPD and echocardiographic aberrant findings (P<0.05), except for left ventricular dysfunction.[3]

The authors are interested in studying the relationship between the severity of COPD and the probability of PH at M. Djamil Hospital, Padang, due to the high probability of PH as a result of chronic hypoxia and inflammation in COPD. Presently, there is a lack of data on patients with PH caused by COPD.

METHODS

This was an analytic descriptive study employing a cross-sectional research design at M. Djamil Hospital, Padang. The study commenced in November 2023 and will continue until February 2024. The study population was stable COPD patients (severe to very severe according to GOLD). The sample size in this study was 64 patients treated at the Tertiary Hospital of M. Djamil General Hospital, Padang, who met the inclusion criteria, namely, patients diagnosed with COPD. The sample was selected using purposive sampling, where the participants were those who were willing to participate in the study and had met certain criteria, such as being between 40–65 years old and having undergone complete examinations, including pulmonary function tests and echocardiography to detect pulmonary hypertension.

The inclusion criteria were patients with severe to very severe stable COPD, both male and female, who came to the pulmonary clinic of M. Djamil Hospital, Padang, willing to participate in all stages of the study by giving written consent and signing the informed consent form. The exclusion criteria were patients with poor echocardiography windows on examination, patients with acute coronary syndrome, patients who had been diagnosed with moderate to severe mitral stenosis, patients with extensive pulmonary fibrosis, and post-lung volume reduction.

The diagnosis of pulmonary hypertension was made using echocardiography or other relevant diagnostic tests to assess the pressure in the pulmonary arteries. The Health Research Ethics Committee (KEPK) of M Djamil General Hospital, Padang, has approved this study with the approval number of DP.04.03/D.XVI.XI/607/2023.

RESULTS

This study included 64 patients with COPD. The characteristics of the subjects were mostly in the age range of 40–65 years (59.4%), male gender (82.2%), elementary school education (29.7%), smokers (81.2%), with a severe Brinkman index (75.0%). The degree of COPD based on spirometry was equal in number between the severe and very severe categories (50.0%), and most of the subjects did not have comorbidities (53.1%).

Table 1. Characteristics of COPD patients at M Djamil Hospital, Padang

Variable	n (%)
Age	
<40 years	2 (3.1)
40–65 years	38 (59.4)
≥65 years	24 (37.5)
Gender	
Male	53 (82.8)
Female	11 (17.2)
Education	
Not in Scholl	7 (10.9)
Junior high school	19 (29.7)
Senior high school	12 (18.8)
High school	13 (20.3)
College	13 (20.3)
Smoking Status	
Smoker	52 (81.2)
Brinkman index (BI)	
BI Mild	3 (4.7)
BI Moderate	1 (1.6)
BI Heavy	48 (75.0)
Non–Smoker	12 (18.8)
Severity COPD	
Severe	32 (50.0)
Very Severe	32 (50.0)
Comorbid	
No comorbid	34 (53.1)
Any comorbid	30 (46.9)

Table 2 presents the association between the risk variables for COPD patients that affect the probability of having pulmonary hypertension. In the age group of under 40 years, both subjects with high probability of PH and low probability of PH had equal percentages (50%, respectively).

Table 2. Association between risk factors affecting the probability of pulmonary hypertension in COPD patients

Risk Factors	Probability of Pulmonary Hypertension (%)			*P*	OR (95% CI)
	Low	Moderate	High		
Ages					
<40 years	1 (50.0)	0 (0.0)	1 (50.0)		
40–65 years	16 (42.1)	4 (10.5)	18 (47.4)	0.908*	---
≥65 years	11 (45.8)	1 (4.2)	12 (50.0)		
Gender					
Male	20 (37.7)	6 (11.3)	27 (50.9)	0.267*	---
Female	7 (63.6)	0 (0.0)	4 (36.4)		
Education					
Not attending school	2 (28.6)	1 (14.3)	4 (57.1)		
Junior high school	8 (42.1)	1 (5.3)	10 (52.6)		
Senior high school	6 (50.0)	2 (16.7)	4 (33.3)	0.813*	---
High school	5 (38.5)	1 (7.7)	7 (53.8)		
College	7 (53.8)	0 (0.0)	6 (46.2)		
Brinkman Index (BI) Smoker					
Severe BI	20 (41.7)	4 (8.3)	24 (50.0)		
Moderate BI	0 (0.0)	1 (100.0)	0 (0.0)	0.010*	1.282 (0.260–6.315)
Mild BI	3 (100.0)	0 (0.0)	0 (0.0)		
Comorbid					
No comorbid	18 (41.9)	4 (9.3)	21 (48.8)	0.785*	---
Any Comorbid	10 (47.6)	1 (4.8)	10 (47.6)		

Note: *Chi-Square test

In the age group of 40-65 years, the majority had a high probability of PH (47.4%), followed by a low probability of PH (42.1%) and a moderate probability (10.5%). Subjects in the age group >65 years mostly had a high probability of PH (50%), followed by low (45.8%) and moderate (4.2%) probability of PH. In the educational status of COPD patients, subjects not attending school, elementary school, and high school, all had a high probability of PH (57.1% vs. 52.6% vs. 53.8%, respectively). Subjects' level of education in high school and college were most likely to have a low probability of PH (50.0% vs. 53.8%).

Severe Brinkman Index mostly had a high probability of PH (50.0%), followed by a low probability of PH (41.7%), and a moderate probability of PH (8.3%). The subject with a moderate Brinkman Index had a moderate probability of PH (100.0%). All subjects with a mild Brinkman Index had a low probability of PH (100.0%). Chronic obstructive pulmonary disease patients who did not have comorbidities experienced a high probability of PH (48.8%), while those with comorbidities experienced low and high probabilities of PH equally (47.6% each). There is a significant correlation between the Brinkman Index and the probability of PH (P<0.05). However, there was no significant relationship between age, gender, educational status, and comorbidities, with the probability of PH (P>0.05).

Chronic obstructive pulmonary disease patients with a severity degree of GOLD 4 mostly experienced a high probability of PH in 17 patients (53.1%), while those with GOLD 3 had a low probability of PH and a high probability of PH in equal number (43.8% each). Nonetheless, there is no significant relationship between the severity of COPD and the probability of PH (P=0.591).

Table 3. Association of COPD severity (airflow limitation) with the probability of pulmonary hypertension

COPD Severity	Probability of Pulmonary Hypertension (%)			*P*
	Low	Moderate	High	
GOLD 4 (very heavy)	13 (40.6)	2 (6.3)	17 (53.1)	0.591*
GOLD 3 (heavy)	14 (43.8)	4 (12.5)	14 (43.8)	

Note: *Chi-Square test

DISCUSSION

Our study determined that the greatest likelihood of pulmonary hypertension was observed in individuals aged 40 to 65 years (47.4%). In comparison, the highest likelihood of low and high pulmonary hypertension was observed in those aged 65 and older (48.0%). These results were in line with

the Shapiro et al study, where PH is more frequent and more severe at the age above 65 years.[4] Pulmonary hypertension is a condition that can affect individuals of all ages, with left heart disease (LHD) being the primary cause, followed by COPD.[5]

According to a meta-analysis, the prevalence of PH in COPD was not significantly influenced by age.[6] Pulmonary hypertension is more prevalent in patients aged 65 years or older, who frequently have cardiovascular comorbidities, according to prior study. In the elderly, there is often an increase in left ventricular diastolic pressure and an increase in estimated systolic pulmonary artery pressure by echocardiography.[7]

This study observed that most male subjects had a high probability of PH (50.9%), while most female subjects had a low probability of PH (63.6%). This finding was in contrast to a study by Sertogullarindan et al, which indicated that female COPD patients developed PH at a more significant rate than their male counterparts. This difference occurred because in that study, women were more at risk of PH due to biomass smoke compared to male COPD cases, which were due to tobacco smoke.[8] Basak et al stated that 95% of male subjects had stable COPD and impaired cardiac function.[9] These results were also in line with a study from Naeije, where female gender was a factor in the probability of pulmonary hypertension, even though women with this condition could survive better than men.[10]

This study was also different from the existing theory, where women were more likely to experience PH. Meta-analysis studies have also demonstrated that females experienced a higher percentage of PH, with prevalence rates varying from 56% to 86%.[5] Females are at a higher risk of developing PH due to their higher cardiac output and lower pulmonary vascular resistance. The modest mean difference in male patients sufficiently produces a 5–8% mortality difference.[11]

The estrogen paradox in PH among women highlights that while they face a greater risk of disease progression, those who are affected tend to respond more favorably to treatment and experience longer survival rates than their male counterparts. The distinct effects of estrogen on pulmonary vasculature and left ventricular performance may elucidate women's vulnerability to pulmonary hypertension.[12]

Based on educational strata, the high probability of PH was seen higher in non-school education (57.1%) and the low probability of PH was observed higher in junior high school (50.0%). Data regarding the association of educational status with the degree of PH is currently unavailable, but existing studies suggest that a person's level of smoking awareness is associated with the incidence of COPD. Education influences awareness of the dangers of smoking.[13] The dependence of smoking on education level is more apparent, with higher education being associated with more controlled COPD disease outcomes than lower education, including the risk of death. Data suggest that socioeconomic factors of non-smoking COPD patients are relevant.[14]

This study, based on smoking status, found that Severe IB has a high risk of pulmonary hypertension and mild IB has a low risk of pulmonary hypertension. There is no data regarding the Brinkman Index and the possibility of pulmonary hypertension. A study by Mohammed et al found that 30.8% of smokers had PH, but it was not statistically significant.[15] This result is almost similar to a study by Jain et al in COPD patients, where most PH were obtained in the low probability (51%), followed by high (26%), and moderate (23%).[16]

Smoking contributes to a rapid elevation in blood pressure and heart rate. Smoking contributes to the development of COPD, chronic bronchitis, and emphysema, which are diseases associated with secondary PH.[17] All degrees of PH involve cigarette smoke. Smokers are prone to COPD and PH, which is multifactorial.[18] COPD and CVD have smoking as a risk factor. Smoking raises the risk of atherosclerosis and systemic inflammation.[18] The inflammatory state in COPD results from the adhesion of leukocytes and other molecules to the endothelium, resulting in damage to the endothelial wall that leads to atherosclerotic plaque formation.[19]

People and animal models have both been shown to develop PH as a result of exposure to

cigarette smoke. Although the cause of PH in smokers is unknown, several studies suggest a role for inducible nitric oxide production (iNOS) and oxidative vascular damage in producing oxidative stress.[20] Chronic hypoxic pulmonary vasoconstriction may induce PH by causing changes that lead to persistent remodelling of the pulmonary vasculature, such as fibromuscular intimal hypertrophy and hypertrophy of the smooth muscle media in arterioles and arteries. Smokers' pulmonary vasculature exhibits the same alterations even in the absence of airflow obstruction.[21]

Cigarette smoke products can cause pulmonary endothelial lesions as an early event in the disease history of PH in COPD. In people with moderate illness, the pulmonary arteries show endothelial dysfunction and changed expression of endothelial-derived mediators that control vascular tone and cell proliferation. Some of these changes are seen in smokers with normal lung function. It is obvious that the higher the Brinkman Index, the greater the risk of pulmonary hypertension.[22]

The main pathophysiological cause of PH is chronic alveolar hypoxia. Chronic hypoxia and hypoxemia, systemic inflammation, atherosclerosis, and pulmonary artery endothelial dysfunction lead to increased pressure in the pulmonary artery, triggering PH. Pulmonary hypertension represents a considerable risk factor for hospitalization and correlates with a reduced life expectancy.[23] The location of residence also influences the occurrence of PH. There is a higher risk of developing PH in COPD patients living in the highlands compared to the lowlands, despite having the same degree of COPD based on the same GOLD criteria.[24]

Pulmonary hypertension is more likely to happen in COPD of GOLD 3 and 4. This is because PH is more closely linked to gas exchange variables or forced expiratory volume in the first second (FEV_1).[25] According to CT imaging, the majority of patients who have COPD-PH have considerable or profound airflow obstruction (GOLD 3 or GOLD 4) or severe emphysema. Additionally, most patients have mild to moderate precapillary pulmonary hypertension (mPAP 21–34 mmHg, cardiac index >2.5 L/min/m^2). Furthermore, individuals with severe COPD typically experience right heart failure, thereby elevating the risk of PH.[26] This study sample predominantly had GOLD 3 and 4, had lower than normal FEV_1 values, and thus a high risk of PH.[27]

LIMITATION

The study had several limitations. The cross-sectional design only provided a snapshot of the relationship between smoking habits and PH, making it difficult to establish causality or track long-term changes. Additionally, other factors, such as comorbidities, diet, or environmental exposures, were not explored but could influence the risk of PH. The Brinkman index measurement was limited, as it did not fully account for the duration, type, or frequency of smoking, which could affect the accuracy of the relationship with PH. The study was also conducted at a single hospital, which might limit the generalizability of the findings. Furthermore, the assessment of COPD severity using the GOLD system was not entirely objective, and additional tests like pulmonary function tests might not have been performed. The reliance on clinical diagnosis of PH might also introduce potential inaccuracies or incomplete assessments. Lastly, uncontrolled confounding factors, such as stress or family history, might have influenced the results.

CONCLUSION

The severity of smoking habits is significantly associated with the risk of PH in COPD patients. Severe BI has a high risk of developing pulmonary hypertension and mild BI has a low risk of developing pulmonary hypertension, suggesting that other factors may play a larger role at higher levels of smoking.

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CONFLICT OF INTEREST

None.

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