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Original Article

Prevalence of Bronchial Hyperreactivity in Stable COPD Patients Treated at Persahabatan Hospital Jakarta, Indonesia (as per GOLD 2017 guidelines)

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Abstract

Background: The Global Initiative of Chronic Lung Disease (GOLD) 2017 has separated spirometric grades (GOLD "1234") from the symptom groups ("ABCD") to improve diagnosis, outcome and therapy for chronic obstructive pulmonary disease (COPD) patients. Bronchial hyperreactivity (BHR) is thought to be a hallmark of asthma, yet it has been observed to occur in COPD. This study aimed to identify BHR in stable COPD patients according to GOLD 2017 grouping.

Methods: This cross-sectional study observed 80 stable COPD patients treated at asthma-COPD clinics in Persahabatan Hospital Jakarta, Indonesia, between May 2018 and March 2019. Diagnosis of COPD was done by spirometry (post-bronchodilator test FEV1/FVC <0.7). Bronchial hyperreactivity was confirmed by PC20 (Provocative Concentration 20), a bronchial challenge test using methacoline <4 mg/mL (FEV1 drop ≥20%). These were performed in all subjects within the inclusion criteria.

Results: Prevalence of BHR in COPD was 73.7% (59/80), wherein 69.7% (46/66) males and 92.9% (13/14) females had BHR in COPD. Bronchial hyperreactivity was found mostly in Group B and Group D (27.1% and 33.9, respectively). Mild BHR was found mostly in Group A and Group D (11.25% and 17.5%, respectively), while moderate-to severe BHR was observed in Group B (11.25%). Airflow limitation was identified mostly in GOLD 2 and 3 (40.7% and 44.1%, respectively). Mild BHR was mostly found in GOLD 2 (20.0%), while moderate-to severe BHR was equally observed in GOLD 2 and 3 (16.25%, both).

Conclusion: Prevalence of BHR in stable COPD patients was 73.7%, and mild BHR was common in stable COPD.

Keywords: Bronchial Hyperreactivity in COPD, Bronchial Provocation Test, Methacoline PC20 Test

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation resulting from airway and/or alveolar abnormalities, usually due to significant exposure to harmful particles or gases.[1] Chronic obstructive pulmonary disease is the 4th leading cause of death in the world and is expected to rank 3rd by 2020. Chronic obstructive pulmonary disease is associated with an economic burden and causes major social problems almost all over the world, especially in developing countries. The number of people with COPD will continue to increase, especially in people over 65 years of age who have comorbid diseases that can aggravate morbidity and mortality.[2,3] The 2017 Global Initiative of Chronic Lung Disease (GOLD) guidelines have separated the spirometric degree (airflow limitation) from the "ABCD" COPD group assessment to refine the diagnosis, prognosis, and treatment of COPD.[1]

Bronchial hyperreactivity is the second most common risk factor for COPD after smoking, affecting 15% of the population.[4] Bronchial hyperreactivity has also been an independent predictor of COPD and respiratory disease mortality in several population-based studies, including as an indicator of a sharp decline in lung function in patients with mild COPD. Bronchial hyperreactivity can be assessed using a bronchial provocation test, which has various examination methods. Bronchial provocation tests can assess the severity of bronchial hyperreactivity in patients with asthma, COPD, and other chronic airway disorders. Understanding the

connection between bronchial hyperreactivity and COPD is essential for improving COPD management, which ultimately reduces morbidity and mortality.[5,6]

It is important to note that the COPD classification framework has evolved since this study was conducted. The 2017 GOLD ABCD assessment tool, which combined symptom burden and exacerbation history into four distinct groups, was revised in the 2023 GOLD report into a simplified three-group ABE system, in which exacerbation history now takes precedence over symptom-severity distinctions. Meanwhile, the underlying spirometric diagnostic criterion has remained unchanged across this revision, meaning the diagnostic basis of the present study remains valid under current guidelines. However, the collapse of the four-group ABCD system into three groups means that group-level associations of the kind examined here, including differences in BHR prevalence across groups ABCD, can no longer be directly replicated using current GOLD classifications. The findings of this study therefore retain value as a phenotype-resolved account of BHR in COPD that predates this simplification, offering a level of granularity that the subsequent GOLD-classified cohort will not reproduce.[7] This study aimed to determine the prevalence of bronchial hyperreactivity in stable COPD patients visiting the Asthma/COPD clinic at Persahabatan Hospital.

Methods

This study was a cross-sectional analytical study conducted at the asthma/COPD clinic of Persahabatan Hospital, Jakarta, from May 2018 to March 2019 on each group of stable COPD patients according to the 2017 GOLD criteria. Sampling was conducted consecutively. Each patient who met the research criteria and was willing to participate was included in the sample until the desired size was reached. The study included stable COPD patients in groups A, B, C, and D, both male and female. These patients visited the asthma/COPD clinic at Persahabatan Hospital and were willing to participate in the study, signing an informed consent form.

The exclusion criteria were patients with exacerbation of COPD; unwillingness to continue after agreeing to participate in the study; patients diagnosed with asthma, other chronic respiratory diseases, and allergic rhinitis; and COPD patients who met the absolute and relative contraindication criteria, including patients with a history of heart attack or stroke in the last 3 months, uncontrolled hypertension with systolic pressure >200 mmHg or diastolic pressure >100 mmHg, aortic aneurysm, inability to perform spirometry techniques properly, pregnancy, breastfeeding, and use of cholinesterase inhibitor drugs for myasthenia gravis.

Subjects meeting the inclusion criteria underwent interviews, physical examinations, spirometry with bronchodilator tests, and bronchial provocation tests with methacholine using the Cockcroft method and the Astograph Jupiter-21 machine for nebulization. The data was then analyzed using SPSS 22.

Among 100 eligible patients screened, 17 declined to participate and 3 did not complete the bronchial provocation test. Therefore, 80 patients who met the inclusion criteria were enrolled in the study and included in the analysis.

This study has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Reference Number 0473/UN2.F1/ETIK/2018).

Results

The study subjects were predominantly male, amounting to 82.5% (66/80). The average age of the subjects in this study was 62.84±8.9 years, with the youngest being 42 years old and the oldest being 83 years old. The highest level of education included secondary education (junior high school and senior high school) and university, which were summarized as higher education at 80% (64/80). The number of subjects who were still working was 43.8% less than the number of subjects who were no longer working, namely 56.3%. A history of smoking was found in 86.3% (69/80) of subjects, with the majority being those who had quit smoking. The Brinkman Index (BI) with a severe degree was the highest at 42.5% (34/69), while the mild and moderate degrees were 13.8% and 30.0%, respectively.

Coughing was the most common daily clinical symptom, accounting for 60%, followed by shortness of breath at 28.8%. The mMRC assessment revealed that 51.3% of subjects had a score of ≥2 (more severe daily symptoms), while the CAT questionnaire found a CAT score of ≥10 at 50%. Based on the body mass index (BMI), overweight was the most common, at 42.5% (34/80), only slightly different from the normal BMI group, at 38.8%.

In the post-bronchodilator lung function examination, the predicted forced expiratory volume in the first second (FEV1% predicted) was 50.39 ± 18.3% and the FEV1/FVC was 54.73 ± 9.9%. Based on the routine use of COPD medication, the use of a combination of long-acting muscarinic drugs (LAMA) with long-acting β2 agonists (LABA) plus inhaled corticosteroids (ICS) was the most common, namely 37.5% (30/80), followed by the use of single LAMA at 30.0%, while the combination of LAMA with LABA was obtained at 16.3%.

Prevalence of Bronchial Hyperreactivity

The prevalence of bronchial hyperreactivity in COPD using methacholine was 73.7% (59/80). The prevalence of bronchial hyperreactivity was then stratified by group and degree of airflow limitation according to the 2017 GOLD guidelines. The highest prevalence of bronchial hyperreactivity was found in group D at 33.9% (20/59), followed by groups B, A, and C at 27.1%, 22%, and 16.9%, respectively.

Meanwhile, the prevalence of bronchial hyperreactivity in the degree of airflow limitation (GOLD) group was highest in group GOLD 3 (severe) at 44.1% (26/59), followed by group GOLD 2 (moderate) at 40.7%.

Relationship of Subject Characteristics to Bronchial Hyperreactivity in COPD

In this study, the characteristics of research subjects experiencing bronchial hyperreactivity were not much different from the characteristics of COPD subjects in general as seen in table 1. In this study, COPD subjects experiencing bronchial hyperreactivity were male at 69.7% (46/66) and female at 92.8% (13/14). The average age of research subjects experiencing bronchial hyperreactivity was 62.94 ± 9.31 years. Based on occupation, the most subjects were unemployed at 57.6% (34/59) while the most educational status was low-educated research subjects at 87.5% (14/16) and high-educated at 70.3% (45/64).

Table 1. Characteristics of research subjects regarding bronchial hyperreactivity in COPD

Variables	BHR (+)	BHR (-)	*P*
	Frequency (%)	Frequency (%)	
Gender			
Male	46 (69.7)	20 (20)	0.09
Female	13 (92.9)	1 (7.1)	
Age (years); Average±SE, Median (min–max)	62.94 ± 9.31	62.52 ± 7.92	0.84
Employment status			
Employed	25 (71.4)	10 (28.6)	0.67
Unemployed	34 (75.6)	11 (24.4)	
Educational Status			
Low-educated	14 (87.5)	2 (12.5)	0.214
High-educated	45 (70.3)	19 (29.7)	
Smoking History			
Smokers	49 (71)	20 (29)	0.27
Non Smokers	10 (90.9)	1 (9.1)	
Brinkman Index (n=69)			
Mild	9 (81.8)	2 (18.2)	0.64
Moderate	16 (66.7)	8 (33.3)	
Severe	24 (70.6)	10 (29.4)	
Symptoms of Chronic Respiratory Tract Disease			
Symptoms	52 (72.2)	20 (27.8)	0.674
No Symptoms	7 (87.5)	1 (12.5)	
mMRC			
<2	27 (69.2)	12 (30.8)	0.370
≥2	32 (78)	9 (22)	
CAT			
<10	28 (70)	12 (30)	0.446
≥10	31 (77.5)	9 (22.5)	
BMI (kg/m^2)			
Underweight	8 (53.3)	7 (46.7)	0.127
Normal	25 (80.6)	6 (19.4)	
Overweight	26 (76.5)	8 (23.5)	

BHR: Bronchial Hyperreactivity

Statistical tests used the Chi-Square and Fisher exact tests

Among COPD subjects with a history of smoking, bronchial hyperreactivity was observed in 71.0% (49/69). The prevalence of bronchial hyperreactivity according to the degree of airway obstruction was 81.8% (9/11) in patients with mild airflow limitation, 66.7% (16/24) in those with moderate airflow limitation, and 70.6% (24/34) in those with severe airflow limitation. Bronchial hyperreactivity was identified in 72.2% (52/72) of subjects who reported daily respiratory symptoms, including cough, dyspnea, and sputum production, compared with 87.5% (7/8) of subjects without these symptoms. Based on nutritional status, bronchial hyperreactivity was present in 76.5% (26/34) of overweight subjects and 80.6% (25/31) of subjects with normal body weight. Statistical analysis demonstrated no significant association between smoking history, degree of airflow limitation, respiratory symptoms, or body mass index and the occurrence of bronchial hyperreactivity among patients with COPD.

Characteristics of the Degree of Bronchial Reactivity in COPD

Mild BHR was most commonly obtained in group D at 17.5% (14/80), followed by group A at 11.25%. In moderate to severe BHR, COPD group B was the most common at 11.25% (9/80). In this study, only one subject was found with a borderline degree or at the threshold of bronchial reactivity, namely in COPD group B at 1.25%. The distribution of data shows that the COPD groups with the most bronchial hyperreactivity were COPD groups B and D at 20% (16/80) and 25% (20/80) respectively, as seen in Figure 1A.

The distribution of COPD based on the degree of airflow limitation was demonstrated to be highest in GOLD 2 and 3, each at 40% (32/80), as seen in Figure 1B. The highest degree of BHR was observed in GOLD 2, especially in the mild degree, at 20%, while the value of the degree of mild and moderate-severe BHR was each found to be equal in GOLD 3, at 16.25%. Researchers then combined GOLD 1 and 2 (mild and moderate) and GOLD 3 and 4 (severe and very severe). Statistical analysis did not identify a significant difference between the airflow limitation classification and bronchial hyperreactivity in COPD.

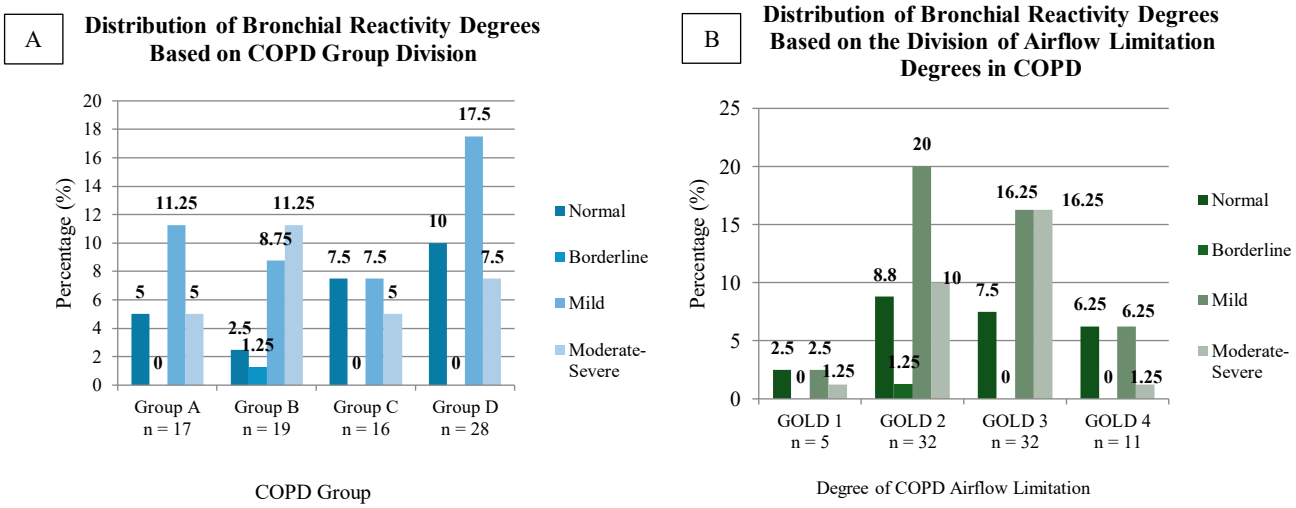

Figure 1. A) Distribution of the degree of bronchial reactivity based on the division of COPD groups; B) Distribution of the degree of bronchial reactivity based on the division of the degree of airflow limitation in COPD

The division of COPD groups based on the history of exacerbations is COPD groups A and B as low-risk groups, namely a history of exacerbations of a maximum of 1 time in a year but not undergoing treatment in the hospital, while COPD groups C and D are high-risk groups that have a history of exacerbations more than 1 time in a year and undergoing treatment in the hospital. Table 2 below shows that COPD groups A and B experienced bronchial hyperreactivity of 80.6% (29/36) while COPD C and D experienced bronchial hyperreactivity of 68.2% (30/44). There was no statistically significant difference obtained in the relationship between bronchial hyperreactivity and COPD based on the history of exacerbations.

The severity of COPD symptoms can be measured using mMRC and CAT. Bronchial hyperreactivity in COPD based on the severity of symptoms in this study showed that groups A and C, which are groups with low symptoms, obtained a percentage of 69.7% (23/33), while in groups B and D it was 76.6% (36/47), as seen in Table 2.

In the COPD grouped based on exacerbation history, it was noted that COPD A and B (low risk) experienced mild bronchial hyperreactivity of 44.4% (16/36), while moderate-severe bronchial hyperreactivity was observed in 36.1% (13/36). In groups C and D (high risk), experienced mild bronchial hyperreactivity of 45.5% (20/44), while the second most was normal bronchial reactivity of 31.8% (14/44). Statistical tests did not find a significant relationship in both groups based on the degree of bronchial reactivity with the COPD group referring to the history of exacerbations, as seen in table 3.

Table 2. Bronchial hyperreactivity in COPD

	Total N (%)	Bronchial Hyperreactivity n (%)		*P*
		BHR (+)	BHR (-)	
COPD based on exacerbation history groups				
Group A + B Low Risk	36 (45)	29 (80.6)	7 (19.4)	0.211
Group C + D High Risk	44 (55)	30 (68.2)	14 (31.8)	
COPD based on the severity of symptoms				
Group A + C Low Symptoms	33 (41.25)	23 (69.7)	10 (30.3)	0.490
Group B + D High Symptoms	47 (58.75)	36 (76.6)	11 (23.4)	

BHR: Bronchial Hyperreactivity
Statistical test using Chi-Square Test

Table 3. Degree of bronchial reactivity in COPD

	Total N (%)	Bronchial Reactivity n (%)			*P*
		Normal	Mild	Moderate–Severe	
COPD based on exacerbation history groups					
Group A + B Low Risk	36 (45)	7 (19.4)	16 (44.4)	13 (36.1)	0.211
Group C + D High Risk	44 (55)	14 (31.8)	20 (45.5)	10 (22.7)	
COPD based on the severity of symptoms					
Group A + C Low Symptoms	33 (41.25)	10 (12.5)	15 (18.75)	8 (10)	0.490
Group B + D High Symptoms	47 (58.75)	11 (13.75)	21 (26.25)	15 (18.75)	

Statistical test using Chi-Square Test

In the grouping of COPD groups referring to the assessment of the severity of these symptoms, mild bronchial hyperreactivity was found to be the most common in each group, namely 45.5% (15/33) in groups A and C which had a CAT value <10 or mMRC <2, while in groups B and D which had a CAT value ≥10 or mMRC ≥2, it was found to be 44.7% (21/47). There were no statistically significant differences found between the two groups, as seen in table 3.

The distribution of COPD based on the degree of airflow limitation was found to be highest in GOLD 2 and 3, each at 40% (32/80), as seen in Figure 1B. The highest degree of bronchial hyperreactivity was observed in GOLD 2, especially in mild degrees, at 20%, while the value of the degree of mild and moderate-severe bronchial hyperreactivity was each found to be equal in GOLD 3, at 16.25%. Researchers then combined GOLD 1 and 2 (mild and moderate) and GOLD 3 and 4 (severe and very severe). However, there were no statistically significant difference between the division of degrees of airflow limitation and bronchial hyperreactivity in COPD ($P = 0.884$).

Characteristics of Bronchial Hyperreactivity Against Pulmonary Function Values in COPD

Lung function includes FVC, FVC (%), FEV1, FEV1 (%), and FEV1/FVC post-bronchodilator. The FVC post-bronchodilator value was seen to be smaller in the study subjects who experienced bronchial hyperreactivity, namely 1.9±0.5 liters, as was seen in the FVC value, namely 1.1±0.4 liters. Meanwhile, the percentage values of FVC, FEV1, and FEV1/FVC were found to be not significantly different between COPD subjects with bronchial hyperreactivity and those without bronchial hyperreactivity. Statistical tests showed no significant difference between all lung function values with $P > 0.05$.

The relationship between the use of inhaled corticosteroids and the incidence of bronchial hyperreactivity in COPD

The use of inhaled corticosteroids (ICS) is a recommended treatment for COPD, especially in high-risk groups such as groups C and D. In this study, 45% (36/80) of subjects received ICS and 72.2% (26/36) experienced bronchial hyperreactivity. A high percentage was also found in the non-ICS group experiencing bronchial hyperreactivity, namely 75% (33/44), as seen in table 4 below. Furthermore, Table 5 explains the distribution of the use of COPD medications containing corticosteroids either alone or in combination with LAMA and/or LABA. The incidence of mild bronchial hyperreactivity was observed most often in subjects using ICS, namely 52.8% (19/36), while the same thing happened in subjects who did not use ICS, namely the most in the non-ICS group at 38.6% (17/55) with a number that was not too different from the moderate-severe degree of 26.3%. No significant difference was found in the statistical test of corticosteroid use in COPD subjects with bronchial hyperreactivity.

Table 4. The relationship between bronchial hyperreactivity and the use of inhaled corticosteroids in COPD

ICS Usage	Total n (%)	Bronchial Hyperreactivity n (%)		*P*
		BHR (+)	BHR (-)	
ICS	36 (45)	26 (72.2)	10 (27.8)	0.779
Non-ICS	44 (55)	33 (75.0)	11 (25.0)	

Statistical test using the Chi-Square test

Table 5. Relationship between Degree of Bronchial Reactivity and Use of Inhaled Corticosteroids in COPD

ICS Usage	Total n (%)	Degree of Bronchial Reactivity n (%)			*P*
		Normal	Mild	Moderate – Severe	
ICS	36 (45)	10 (27.8)	19 (52.8)	7 (19.4)	0.233
Non-ICS	44 (55)	11 (25.0)	17 (38.6)	16 (26.3)	

Statistical test using the Chi-Square test

Discussion

Bronchial hyperreactivity, although often associated with asthma, is an independent risk factor for COPD, alongside a history of smoking, affecting 15% of the population.

Bronchial hyperreactivity is also said to be a marker of the risk of excessive decline in lung function in patients with mild COPD. In the general population, bronchial hyperreactivity by the methacholine test is found in approximately 10–16% of adults.[8] Research in Indonesia on bronchial hyperreactivity in COPD was conducted in 1989 by Yunus et al., with a frequency of 76.7%.[9]

Bronchial provocation testing using methacholine is one method used to assess bronchial hyperreactivity in patients with airflow limitation such as COPD because it has fewer side effects compared to the use of histamine. This study was conducted to determine the prevalence of bronchial hyperreactivity in COPD using the 2017 GOLD guidelines, which have divided the diagnosis of COPD into two major parts: based on the severity of symptoms and history of exacerbations and based on airflow limitation or decreased lung function after bronchodilators.

Prevalence of Bronchial Hyperreactivity in COPD

This study yielded a prevalence of bronchial hyperreactivity in COPD of 73.7%. This prevalence value is almost the same as the study conducted by Yunus et al. at Persahabatan Hospital in 1989, which was 76%, although the number of samples used in the study was only 30 samples.[9] Furthermore, a study by Tashkin et al. in the United States entitled The Lung Health Study in 1992 reported a slightly lower prevalence of bronchial hyperreactivity, namely 60%.[6] The study entitled GLUCOLD in the Netherlands in 2009 obtained a higher prevalence of up to 94%, and a study in Japan by Koyama et al. in 1994 found a prevalence of 83%.[10,11]

The GLUCOLD study only recruited moderate-to-severe COPD patients with a history of smoking and steroid use, while this study recruited all COPD groups, although the comparison between COPD groups was not balanced. Trofimenko and Chernyak's study obtained results that were almost similar to this study, namely the prevalence of bronchial hyperreactivity in COPD was 69% of 75 subjects.[12] This study also used a bronchial provocation test with methacholine, but only subjects with moderate-to-severe COPD or GOLD 2. The variation in the prevalence of bronchial hyperreactivity in COPD worldwide is likely due to several factors, such as the number of samples and the degree of COPD recruited, as well as the choice of bronchial provocation tests, which can be performed using various methods.

Other studies on bronchial hyperreactivity in COPD have used other modalities as the basis of examination, such as the use of histamine (Provocating Dose 20/PD20) in a study by Yan et al. in 1985 in Western Australia, which noted that 50% of 59 subjects with COPD experienced bronchial hyperreactivity.[13] Leuppi et al. in Sweden used mannitol and histamine in a bronchial provocation test on 30 research samples. All samples experienced bronchial hyperreactivity in the use of histamine, while only 23% of samples experienced bronchial hyperreactivity using mannitol.[14] In addition, there are many other modalities that can be used to see bronchial hyperreactivity in COPD, including exercise tests, 4.5% NaCl solution (concentrated), acetaldehyde, propranolol, air hyperventilation, and so on. However, the use of methacholine is a safe, non-specific substance with fewer side effects than histamine.

Prevalence of bronchial hyperreactivity by COPD group classification

In this study, the COPD group D was described to have the highest bronchial hyperreactivity, namely around 33.9% (20/59), followed by COPD group B at 27.1% (16/59). Almost the same prevalence was found in the study by Dima et al., which only involved mild and moderate COPD as determined by the GOLD grade or airflow limitation. However, the study was conducted in 2010 when the GOLD guidelines still combined COPD groups based on the history of exacerbations and symptom severity with the GOLD grade or airflow limitation. Therefore, it can be concluded that the COPD groups in the Dima et al. study were groups A and B.[15] Meanwhile, in this study, bronchial hyperreactivity was found at 25% (4/10) using methacholine. Regardless of the degree of airflow limitation in COPD, groups B and D are COPD with a CAT score ≥10 or mMRC ≥2, so it seems that bronchial hyperreactivity tends to occur in the COPD group with a history of more severe daily symptoms.

Based on the Severity of COPD Symptoms

The COPD diagnosis in GOLD 2017 separates COPD groups based on exacerbation history, hospitalization, and symptom severity into groups A, B, C, and D. When grouping based on symptoms, COPD groups can be separated into groups A and C, which have a history of mild daily symptoms, and also groups B and D, which have a history of severe daily symptoms. This can be measured using the mMRC and CAT scores. This study revealed that the distribution of COPD subjects in groups A + C was lower than in groups B + D, at 41.25% and 58.75%, respectively. This study further pointed out that the incidence of bronchial hyperreactivity in groups A + C was mostly mild, at 18.75%. The same was true in groups B + D, with a percentage of 26.25%. Statistical testing did not reveal a significant relationship between the two groups in terms of bronchial reactivity, with a *P*-value >0.05.

The reason why mild bronchial hyperreactivity is more common in COPD has not been fully explained, but several reviews suggest that the mechanism of bronchial hyperreactivity in COPD is due to geometric phenomena in the airway muscles, which result in narrowing of the airway caliber. Meanwhile, mast cell activation is not as severe as in asthmatic patients undergoing bronchial provocation testing. Furthermore, inflammatory factors in COPD patients experiencing bronchial hyperreactivity are not as prominent as in asthmatic patients, resulting in differences in the degree of bronchial hyperreactivity in asthma and COPD.[11,16]

Mild bronchial hyperreactivity is indicated by PC20 values >1 mg/ml and <4.0 mg/ml. However, the higher values in groups B + D indicate that bronchial hyperreactivity tends to occur in the more severe COPD group. Nevertheless, Zanini et al. in their research stated that bronchial hyperreactivity in COPD was negatively correlated with assessments based on symptom scores (rs = -0.76, $P = 0.005$).[17] Until now, there has been no previous research that specifically shows the distribution and relationship of the degree of bronchial reactivity in COPD patients from the perspective of COPD group division according to GOLD 2017.

Based on COPD Exacerbation History

History of exacerbations and hospitalizations divided the COPD groups into Group A+B, with no or only one exacerbation without hospitalization, and Group C+D, with at least one exacerbation in the past year and a history of hospitalization due to COPD. This study acknowledged that the percentage of COPD in Group C+D was higher than in Group A+B, at 55%. Mild bronchial hyperreactivity was the most common among the two groups, at 45%.

The second highest percentage of moderate to severe bronchial hyperreactivity, at 36.1%, was found in Group A+B, while Group C+D had the second highest value for normal bronchial reactivity. However, no association was obtained between bronchial hyperreactivity and COPD group division based on history of exacerbations or hospitalizations ($P >0.05$). Zanini et al. in their study involving 29 COPD patients suggested that the frequency of exacerbations in the past year did not have a positive relationship with the degree of bronchial hyperreactivity (rs = -0.59, $P = 0.005$) as well as with assessments based on symptom scores (rs = -0.76, $P = 0.005$).[17]

Prevalence of bronchial hyperreactivity based on COPD airflow limitation

The COPD diagnostic assessment in GOLD 2017 compared to GOLD 2011 has undergone significant changes, including the separation of the "ABCD" group assessment between spirometric degree or airflow limitation and daily symptom severity and history of exacerbations in the past year. The degree of airflow limitation is a good predictor of mortality and other important health outcomes, while the "ABCD" group is associated with pharmacotherapy recommendations, which in GOLD 2017 were exclusively assessed based on patient symptoms and history of COPD exacerbations. The assessment of airflow limitation severity is presented in the GOLD "1234" format.[1]

In this study, the percentage of bronchial hyperreactivity in COPD based on the degree of airflow limitation was highest in GOLD 3 and 2, at 44.1% (26/59) and 40.7% (24/59), respectively. GOLD 2 and 3 can be considered as moderate and severe COPD groups. Existing studies generally include people with mild to moderate COPD and rarely those with severe COPD due to the low FEV1 value in very severe COPD, which is <30%. A 2015 study by Zanini et al. in Italy identified that 41.3% (12/29) experienced bronchial hyperreactivity using the methacholine test, but only mild and moderate COPD were included in this study.[17]

Cockcroft and Davis stated that the majority of patients with moderate to severe COPD will experience bronchial hyperreactivity using direct stimulation, and this figure decreases by approximately 25 to 50% in patients with lower levels of COPD. It is said that the geometric phenomenon determines the occurrence of bronchial hyperreactivity in COPD due to direct stimulation in the bronchial provocation test, which is strongly correlated with reduced airway caliber.[18] This study included 11 subjects with very severe COPD or GOLD 4, but only 5 subjects experienced bronchial hyperreactivity, and none of the subjects experienced severe side effects after the bronchial provocation test.

Demographic Characteristics of Bronchial Hyperreactivity in COPD

Overall, more males (82.5%) were obtained among the subjects with COPD in this study, however, only 69.7% of these male subjects experienced bronchial hyperreactivity. This study's results are similar to those of Trofimenko and Chernyak's 2015 study, which reported a COPD prevalence of 85.6% in men. In the study by Trofimenko and Chernyak, a lower prevalence was found in men, 66.6% (20/30), and in the study by Yan et al., namely 76%.[12,13]

A larger study by Tashkin et al., entitled The Lung Health Study, noted a higher COPD prevalence in women, at 85.1%. Kanner et al., also included in the Lung Health Study, stated that women with COPD experienced more severe bronchial hyperreactivity than men, even after adjusting for baseline airway obstruction.[6,19] This study indicated that the percentage of bronchial hyperreactivity among female subjects diagnosed with COPD was 92.85% (13/14), with only one female subject experiencing borderline bronchial reactivity (PC20 = 8 mg/L).

In this study, there were three female subjects who smoked with severe and very severe COPD according to the 2017 GOLD criteria. Several hypotheses suggest that the size of the female airway caliber correlates with the incidence of bronchial hyperreactivity, as well as a history of smoking with severity in women. Tashkin et al. explained that the influence of gender on the incidence of bronchial hyperreactivity in COPD remains unclear but may be related to age differences between men and women, smoking history, the presence of asthma, or baseline airway obstruction.[6]

Han et al. acknowledged that there is increasing evidence that women are more likely to develop COPD than men.[20] A meta-analysis conducted by Gan et al. observed that women who smoke experience a more rapid decline in lung function than men between the ages of 45 and 50, leading to a more rapid progression of COPD.[21] However, our study only involved a small number of female COPD subjects, so further research is needed with a larger number of subjects, particularly involving women.

The overall mean age of COPD subjects in this study was 62.83±8.9 years, with a range of ages from 42 to 83 years. Similar results were seen in the study by Yan et al., namely 62.7±11.1 years, and in the study by Leuppi, which found an age range of 44 to 83 years.[13,14] Nonetheless, the study by Dima et al. revealed a slightly lower age population, namely 58.4±2 years, as did the study by Trofimenko, which noted a COPD age population of 58 years.[15,22] The average age of COPD subjects who experienced bronchial hyperreactivity compared to those who did not experience bronchial hyperreactivity in this study did not differ from the average age of COPD as a whole, similar to the study by Trofimenko and Chernyak.[22]

Basically, when a person reaches the age of 35–40 years, the aging process will occur, characterized by a decrease in FEV1 values of 30 ml/year in men and 23 ml/year in women, although there is some variability assessed individually.[23,24] On the other hand, risk factors such as smoking and the occurrence of bronchial hyperreactivity can accelerate the decline in lung function, especially in patients with COPD. A systematic literature review by Schichilone et al. in 2005 on bronchial hyperreactivity in the elderly identified that 10 of 18 studies concluded a positive association between bronchial hyperreactivity and aging, although the studies did not specifically distinguish between asthma and COPD. Additionally, the average number of COPD patients was higher than that of asthma patients because the studies were conducted on individuals aged over 65 years.[25]

This study involved the largest number of subjects with higher education (secondary and university), at 80%. Similarly, the COPD study by Scott et al. stated that 64% of COPD subjects had completed secondary education.[26] A study by Hetlevik et al. in Norway found results quite similar to ours, indicating that COPD patients were more likely to have primary education (<13 years) compared to those with secondary and continuing education (>16 years).[27] Research by Lange et al. in Denmark hypothesized a relationship between shorter education and smoking history, higher prevalence of respiratory symptoms, and lower predicted VEP1 % values with P <0.01.[28]

The percentage of COPD subjects experiencing bronchial hyperreactivity in this study had a high level of education (70.3%), while a higher rate was observed in subjects with low levels of education (87.5%). Statistical tests did not find a significant association between the incidence of bronchial hyperreactivity and educational status. Low socioeconomic status is a clear risk factor for COPD because it is intrinsically linked to other risk factors such as low birth weight, nutritional status, access to healthcare, respiratory infections, and smoking history. The association between educational status and bronchial hyperreactivity in COPD is not a direct one but rather an indirect one when combined with smoking history, which is positively correlated with education level and more rapid lung function decline. However, to date, no previous studies have specifically examined the association between socioeconomic status, including education, and the incidence of bronchial hyperreactivity in COPD.[29]

In this study, the majority of COPD subjects were unemployed (56.3%). Research by Kumbhare et al. in the United States analyzed that the unemployed COPD group was higher, at 76.3%.[30] The high number of unemployed subjects was due to the age of the COPD patients in this study having reached retirement age, and the female subjects were predominantly housewives. However, in contrast, research by Baarnes et al. in Denmark revealed a much lower value for unemployed subjects, at 21.7%.[31] Several jobs in our study subjects could be categorized as occupational exposure, including construction workers, public transportation drivers, and cleaners, although these were not discussed in depth in this study. Baarnes et al. also categorized several jobs as occupational exposure and must meet the requirement of >1 year of exposure. Baarnes et al. found a relationship between occupational exposure and COPD with a Hazard Ratio (HR) of 1.29 (95% CI 1.18–1.41).[31] To date, we have not obtained any previous research linking the occurrence of bronchial hyperreactivity in COPD with work or occupational exposure. This study noted that 86.3% of the subjects had a history of smoking, and almost all were male. Bronchial hyperreactivity was seen in 71% of the smokers and 90.9% of the nonsmokers. All nonsmoking COPD subjects were female. Statistical tests in this study demonstrated no significant difference between bronchial hyperreactivity in COPD and smoking status. Several large-scale studies have supported that smoking is a risk factor for bronchial hyperreactivity.[32]

Willemse et al. reported that smoking-induced COPD is associated with decreased lung function and bronchial hyperreactivity using both direct bronchial provocation tests using methacholine and indirect tests using adenosine-5'-monophosphate (AMP). Another cross-sectional study showed no difference in bronchial hyperreactivity with histamine or methacholine between former and current smokers with COPD.[33,34] Nonetheless, Wise et al. explained that bronchial hyperreactivity with methacholine in COPD worsened after 5 years of smoking compared to COPD patients who had quit smoking, but aging cannot be ignored in COPD patients.[35]

This study observed moderate and severe IB in 30% and 42.5%, respectively, in COPD subjects with a history of smoking. Furthermore, mild, moderate, and severe IB was most common in COPD subjects with bronchial hyperreactivity, at 81.8%, 66.7%, and 70.6%, respectively. Statistical testing did not reveal any significant differences. Kojima et al. suggested that age and smoking habits are strong risk factors for the occurrence of COPD.[36] A study in South Korea found an OR of 3.2 in study subjects in smokers with IB >400 compared to non-smokers for decreased lung function (FEV1/FVC <75%).[37] Meanwhile, a study in Greece reported that the OR after age adjustment in COPD with a history of smoking (IB ≥300) compared to smokers with IB <300 was 1.5 in men and 4.7 in women.[38]

Pulmonary Function Characteristics in COPD with Bronchial Hyperreactivity

In this study, lung function characteristics included FVC, FVC%, FEV1, FEV1%, and FEV1/FVC. In general, the lung function values of COPD patients in this study were much lower than those of the studies by Zanini et al. and Leuppi et al. This is due to the subjects recruited for this study included subjects with mild to very severe COPD. Meanwhile, the study by Zanini et al. only recruited patients with mild to moderate COPD, and the study by Leuppi et al. recruited patients with severe or GOLD 3 degrees.[14,17] Lung function values in COPD subjects with bronchial hyperreactivity appeared slightly different from those without bronchial hyperreactivity. The FVC and FEV1 results appeared lower than those without bronchial hyperreactivity, but conversely, there were higher results in FVC%, FEV1%, and FEV1/FVC values. These results contradict the theory that bronchial hyperreactivity in COPD is associated with a more rapid decline in lung function.[6]

Characteristics of Corticosteroid Drug Use in COPD with Bronchial Hyperreactivity

This study has shown that 72% subjects in group C and D who received inhaled corticosteroid based on 2017 GOLD COPD guidelines, were more likely to have bronchial hyperreactivity.[1] However, an almost similar number (75%) also found in COPD group A and B where no inhaled corticosteroid has been given to these groups.

This study specifically stratified the degree of bronchial reactivity in COPD and noted that mild bronchial hyperreactivity was the most common in both the ICS and non-ICS groups. However, this study did not specifically link the use of inhaled corticosteroids in COPD to bronchial hyperreactivity. A study by Soeratman et al. at Persahabatan Hospital in 1992 concluded that there was a reduction in bronchial hyperreactivity in COPD using oral beclomethasone dipropionate, but the treatment benefit was no longer apparent after 4 weeks of discontinuation.[39] A study by Verhoeven et al. supported that the effect of inhaled corticosteroids was not significant on the incidence of bronchial hyperreactivity in COPD compared to asthma.[40] Meanwhile, the Lung Health Study investigated the use of inhaled triamcinolone for 9 and 33 months and reported that it could reduce the incidence of bronchial hyperreactivity in COPD.[41]

To date, no research on bronchial hyperreactivity in COPD, especially using the GOLD guidelines above 2017, has been conducted, to our knowledge, especially in Southeast Asia. Therefore, our results can complement the existing global data on bronchial hyperreactivity in COPD, especially in Asia. Furthermore, our study included patients with very severe COPD or those with a post-BD FEV1 value <30% of predicted. We chose this because previous studies excluded patients with very severe COPD due to FEV1 values <1000 ml. It is an absolute contraindication for bronchial provocation testing using methacholine, according to the 1999 American Thoracic Society guidelines. However, these guidelines were specifically developed for bronchial provocation testing in asthma.

To date, there are no specific guidelines for bronchial provocation testing for COPD, and there have been no reports of adverse effects from methacholine that are dangerous to patients and can even cause death. None of the 80 participants in our study experienced severe, life-threatening side effects. Some only experienced symptoms such as chest tightness, shortness of breath, fatigue, and wheezing after the test. Inhaled salbutamol, 400 µg, was administered to all participants who experienced side effects after the bronchial provocation test. The prevalence results in this study can be considered true prevalence. Several difficulties or obstacles in this study include the decreasing number of COPD samples at Persahabatan General Hospital due to the National Health Insurance referral system, which prevents many COPD patients from seeking treatment at Persahabatan's network hospitals as tertiary referral hospitals. Moreover, the age of COPD patients is increasingly advanced, namely over 65 years old. For this reason, some patients were forget to stop using their daily inhalers before underwent the bronchial provocation tests, requiring rescheduling. Some COPD patients also experienced severe shortness of breath. Another issue was the technical problems with the Jupiter-21 Astograph machine, which experienced several interruptions, delaying the bronchial provocation test for several days. A weakness we obtained in this study was the cross-sectional design, which could not assess the causal relationship between bronchial hyperreactivity and COPD risk factors, so a prospective study design is needed. Recall bias can occur in this study, especially during interviews, because research subjects did not accurately provide a history of exacerbations and daily respiratory symptoms, especially when assessing mMRC and CAT scores.

Conclusion

Based on the research results, the prevalence of bronchial hyperreactivity in COPD patients examined using methacholine was 73.7%. The prevalence of bronchial hyperreactivity in each COPD stage showed variations, namely in group A at 22%, group B 27.1%, group C 16.9%, and group D 33.9%. Based on the degree of airflow limitation according to the GOLD classification, the prevalence of bronchial hyperreactivity was found in GOLD 1 at 15.1%, GOLD 2 at 40.7%, GOLD 3 at 44.1%, and GOLD 4 at 10.2%. Statistical analysis showed no significant relationship between bronchial hyperreactivity and the division of COPD based on group or degree of airflow limitation. In addition, no significant relationship was found between bronchial hyperreactivity and patient characteristics, including gender, age, educational history, occupational history, body mass index (BMI), or smoking status. Decreased lung function was also not significantly associated with bronchial hyperreactivity in COPD. Similarly, inhaled corticosteroid use

did not show a significant association with the incidence of bronchial hyperreactivity in COPD patients.

As a recommendation, sputum examination and blood eosinophil levels in study subjects experiencing bronchial hyperreactivity are needed to assess the likelihood of an asthma-COPD overlap diagnosis. Furthermore, prospective studies with larger sample sizes are needed, including standardized bronchial provocation tests in COPD and assessment of bronchial hyperreactivity, considering the possibility of a COPD phenotype manifested by bronchial hyperreactivity.

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