Vol. 1, No. 2, Februari 2021

e-ISSN 2474-1306

Official Journal of The Indonesian Society of Respirology

RESPIRATORY Science

Website: http://www.jurnalrespilogi.org

RESPIRATORY Science

Official Journal of The Indonesian Society of Respirology

Editorial Office
The Indonesian Society of Respirology
Jl. Cipinang Bunder, No. 19, Cipinang, Pulo Gadung
Jakarta Timur, Indonesia, 13240 Telp: 02122474845
Email: editor@respiratoryscience.or.id
Website: https://respiratoryscience.or.id/

Publisher
The Indonesian Society of Respirology

RESPIRATORY Science

Official Journal of The Indonesian Society of Respirology

VOLUME 1, NOMOR 2, October 2020

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ORIGINAL ARTICLE

New GOLD COPD Guideline 2019: How We Deal With It? (Inhaled Corticosteroid Use and Blood Eosinophil Count)

Ari Julian Saputra*[,1], Kiki Widyastuti[1,2] Yusup Subagio Sutanto[3]

[1]Bukit Asam Medika Hospital, Tanjung Enim
[2]dr. H. Moh. Rabain Regional Public Hospital, Muara Enim
[3]Departement Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Sebelas Maret - dr. Moewardi Hospital, Solo

ABSTRACT

Background: Blood eosinophils may predict response to inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD), where ICS is recommended in patients at high risk of exacerbations by the Global Initiative for COPD (GOLD) strategy. It can help clinicians to estimate the likelihood of beneficial preventive responses to the addition ICS to regular bronchodilator treatment, and thus can be used as a biomarker in conjunction with clinical assessment when making decisions regarding ICS use. This study aims to compare therapeutic data with blood eosinophil count in COPD patients.

Method: Data were collected from consecutive COPD outpatients in Bukit Asam Medika Hospital starting from March 1st, 2019 until June 30th, 2019 and dr. H. Mohamad Rabain Hospital starting from Oct 1st, 2019 until Dec 27th, 2019. We collected demographics, anthropometrics, smoking history, therapy, dynamic lung volumes, the Medical Research Council scale (MRC), CAT score, and blood eosinophil count.

Results: From 57 data collected, 24 patients (42,1%) were having blood eosinophil count ≥300. Patients who have more exacerbation in COPD Group C were 33,3% and 63,2% in COPD Group D. The proportions of ICS-treated COPD Group D patients and blood eosinophil count of <300 and ≥300 was 63,9% and 36,1%, respectively.

Conclusion: This study may provide information and characteristic of COPD patient in Indonesia rural area and showed who may have benefit to ICS therapy based on recommendation GOLD COPD 2019. Blood eosinophils counts is a low-cost biomarker and may help clinicians to made decision therapy.

Keywords: COPD, ICS, blood eosinophil count

*Correspondence: Ari Julian Saputra - arijulian94@gmail.com

Submitted: January 13th 2021, Accepted: February 13th 2021, Published: February 28th 2021

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial. In 2010, the number of COPD cases was 384 million with a global prevalence of 11,7%. Globally, there are around three million deaths annually.[1–4]

Exacerbations in COPD are major contributors to worsening lung function, impaired quality of life, emergency healthcare use and COPD-related mortality.[5] Regular use of inhaled corticosteroids (ICS), either alone or in combination with a long-acting β2-agonist (LABA), reduces the risk of chronic obstructive pulmonary disease (COPD) exacerbation. These drugs are effective agents for the prevention of COPD exacerbations and improvement of lung function. They also have various effects on health status, but they are associated with adverse events, as pneumonia being the most concerning.[6]

Several recent studies have shown that blood eosinophil counts predict the magnitude of the effect of ICS (added on top of regular maintenance bronchodilator treatment) in preventing future exacerbation. Therefore, in Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019, blood eosinophil counts can help clinicians estimate the likelihood of a beneficial preventive response to the addition of ICS to regular bronchodilator treatment, and thus can be used as a biomarker in conjunction with clinical assessment when making decisions regarding ICS use.[1]

Indonesia do not yet have definitive data of COPD prevalence. The survey results of non-communicable diseases by the General Directorate of Eradication of Non-Communicable Diseases in five provincial hospitals in Indonesia (West Java, Central Java, East Java, Lampung, and South Sumatra) in 2004, COPD contributes at the most to morbidity (35%), followed by bronchial asthma (33%), lung cancer (30%), and other 2%.[7] As the GOLD 2019 application, this study aims to compare therapeutic data with blood eosinophil count in COPD patients.

METHOD

The research will be conducted in an observational descriptive from consecutive COPD outpatients in Bukit Asam Medika Hospital starting from March 1st, 2019 until June 30th, 2019 and Dr. H. Mohamad Rabain Hospital starting from Oct 1st, 2019 until Dec 27th, 2019.

Study participants will be patients suffering from COPD as defined by the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines,[1] more than ≥40 years old, recruited from Bukit Asam Medika Hospital, Tanjung Enim, Muara Enim District, South Sumatra, Indonesia between 1 March until 30 June 2019 and Dr. H. Mohamad Rabain Hospital Muara Enim District, South Sumatra, Indonesia between 1 October until 27 December 2019. Patients will be excluded for refusal to participate, cannot perform spirometry, and unwilling or unable to provide informed consent.

The following data and measurements will be recorded:

- Demographics and anthropometrics, smoking history, and drug therapy.
- Dynamic lung volumes, assessed after bronchodilation and expressed as absolute and percent of predicted values according to The Pneumomobile Project Indonesia.
- The subjective sensation of breathlessness will be evaluated by means of the Medical Research Council (MRC) scale.
- Indonesian Version of the COPD Assessment Test (CAT) score.
- Blood eosinophil count.

RESULT

This study describes the main parameters namely therapeutic data and blood eosinophils in COPD patients, as well as several characteristics. These characteristics include gender, age, education, Brinkman index, duration of diagnosis, nutritional status (BMI), degree classification based on GOLD, and COPD group. There are 57 patients has been assessment. The characteristics of research subjects can be seen in Table 1.

The range age of the population was 55 until 64 years; approximately 96,5% of respondents were male. The most research population is junior high school education (33,3%). Brinkman index of patients is dominated by moderate and heavy. Most of respondents were old patient. Respondents with body mass index underweight was 45,6% and normal weight was 43,9%. Respondents with GOLD I, II, III, and IV constituted 7,0%, 36,8%, 38,6%, and 17,5% of the population, respectively. Respondents in group A same with group B is 1,8% and groups C, D constituted 33,3% and 63,2% of the population, respectively. In blood eosinophil count <300 cells/µL was 57,9%.

Table 1. Characteristics of COPD Patient

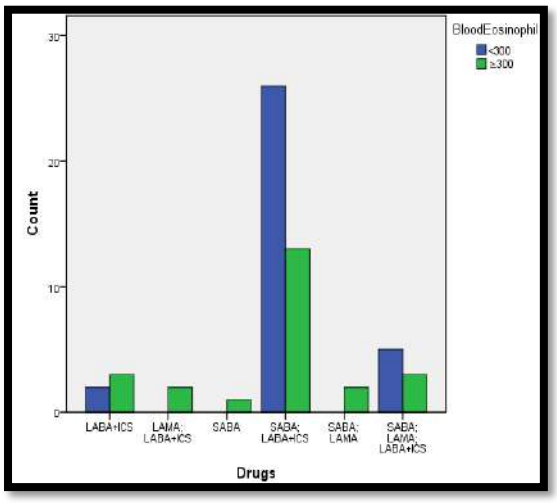
Variable	Frequency	Percent
Sex		
Man	55	96.5
Woman	2	3.5
Age		
40-54	13	22.8
55-64	25	43.9
65-69	10	17.5
≥70	9	15.8
Education		
Uneducated	14	24.6
Elementary School	7	12.3
Junior High School	19	33.3
Senior High School	15	26.3
Diploma	1	1.8
Master Degree	1	1.8
Brinkman Index		
Never	5	8.8
Mild	1	1.8
Moderate	26	45.6
Heavy	25	43.9
Duration of Diagnosis		
New	25	43.9
Old	32	56.1
Body Mass Index		
Underweight	26	45.6
Normal weight	25	43.9
Overweight	5	8.8
Obesity	1	1.8
GOLD		
I	4	7.0
II	21	36.8
III	22	38.6
IV	10	17.5
COPD Group		
A	1	1.8
B	1	1.8
C	19	33.3
D	36	63.2

Table 1. Characteristics of COPD Patient (cont.)

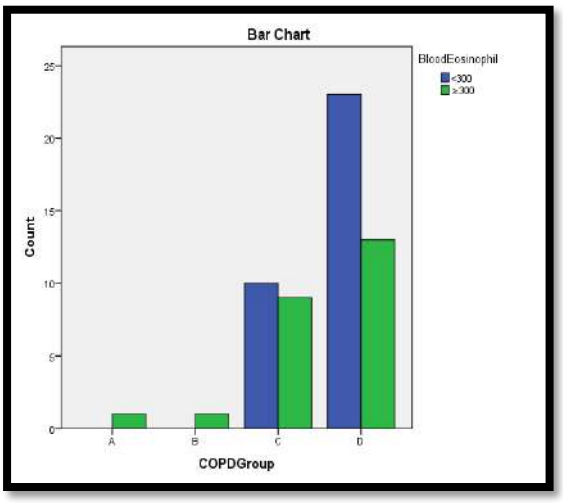
Variable	Frequency	Percent
Blood Eosinophil		
<300	33	57.9
≥300	24	42.1
Drugs		
SABA	1	1.8
LABA+ICS	5	8.8
SABA; LABA+ICS	39	68.4
SABA; LAMA	2	3.5
LAMA; LABA+ICS	2	3.5
SABA; LAMA; LABA+ICS	8	14.0

Table 2. Drugs and COPD Group Crosstabulation

Drugs	Blood Eosinophil		Total
	<300	≥300	
LABA+ICS	2 (6.1%)	3 (12.5%)	5 (8.8%)
LAMA; LABA+ICS	0 (0.0%)	2 (8.3%)	2 (3.5%)
SABA	0 (0.0%)	1 (4.2%)	1 (1.8%)
SABA; LABA+ICS	26 (78.8%)	13 (54.2%)	39 (68.4%)
SABA; LAMA	0 (0.0%)	2 (8.3%)	2 (3.5%)
SABA; LAMA; LABA+ICS	5 (15.2%)	3 (12.5%)	8 (14.0%)
Total	33 (100.0%)	24 (100.0%)	57 (100.0%)



Graphic 1. Drugs Distribution by Blood Eosinophil Count



Graphic 2. Blood Eosinophil Count by COPD Group

The proportions of COPD patients who had an inhaler drug are shown in Table 2.

In group A there were 1 respondent (2.9%) using SABA, and group B 1 (2.9%) respondent using

SABA; LABA + ICS. 10 (29.4%) of respondents in group C were divided into 7 respondents (20.6%) using SABA; LABA + ICS, 2 (5.9%) of respondents use SABA; LAMA, and 1 respondent (2.9%) use triple therapy. Therapy in group D is dominated by SABA; LABA + ICS were 16 (47.1%) respondents while 6 (17.6%) respondents used triple therapy. ICS is recommended in patients at high risk of exacerbations by the Global Initiative for COPD (GOLD) strategy. The highest use of ICS in group D was 22 respondents (64.7%).

Comparison between ICS use and Blood Eosinophil Count can be seen in Graph 1. Respondents who received single ICS therapy is 3 (60%) of 5 respondents and ICS in dual therapy is 15 (57.7%) of 26 respondents who had a blood eosinophil count ≥300 cells/μL. While respondents who received ICS in triple therapy with blood eosinophil count ≥300 cells/μL are 3 (37.5%) of 8 respondents.

Graphic 2 shows the proportions of blood eosinophil count by COPD group patients. There was a higher proportion of respondents with blood eosinophil counts of ≥300 cells/μL in COPD Group D 13 (36,1%) respondents. But compared with blood eosinophil count <300 cells/μL in COPD Group D, higher than blood eosinophil counts of ≥300 cells/μL is 23 (63,9%) respondent. The proportions of respondents with blood eosinophil counts of ≥300 cells/μL in COPD Group A, B, and C were 1 (4,2%) respondent, 1 (4,2%) respondent, and 9 (37,5%) respondent, respectively.

DISCUSSION

This study shows therapeutic data, blood eosinophils count, and several characteristics in COPD patients. These characteristics include gender, age, education, Brinkman index, duration of diagnosis, nutritional status (BMI), degree classification based on GOLD, and COPD group. The efficacy, safety and positioning of ICS in the treatment of patients with COPD is much debated, since it can result in clear clinical benefits in some patients ("friend") but can be ineffective or even associated with undesired side effects, *e.g.* pneumonia, in others ("foe").[8]

The use of blood eosinophils as a biomarker in COPD is based on the premise that they reflect and correlate with tissue eosinophilic inflammation in pulmonary airways and parenchyma.[9] *Post hoc* and pre-specified analyses of chronic obstructive pulmonary disease (COPD) randomized controlled trials have shown that higher blood eosinophil counts predict greater

inhaled corticosteroid (ICS) effects on exacerbation prevention.[10] The clinical relevance of a blood eosinophil cut off in the management of COPD remains uncertain because blood eosinophils are not stable throughout the disease course. A recent publication reported that the association of higher eosinophil counts with exacerbations is not consistent.[11]

The rate of pneumonia was marginally higher in those with <2% blood eosinophils than those with ≥2% blood eosinophils, echoing findings from a *post hoc* analysis that suggested rates of pneumonia were slightly lower in patients with COPD with higher eosinophil counts and putatively more responsive to ICS.[1,12] The threshold of a blood eosinophil count > 300 cells/µL identifies the top of the continuous relationship between eosinophils and ICS, and can be used to identify patients with the greatest likelihood of treatment benefit with ICS.[1] The IMPACT trial and observational study in UK and US patients with COPD shows that assessment of blood eosinophil count and smoking status has the potential to optimize ICS use in clinical practice in patients with COPD and a history of exacerbations and should be considered while making treatment decisions.[13,14]

The use of blood eosinophil counts to predict ICS effects should always be combined with clinical assessment of exacerbation risk (as indicated by the previous history of exacerbations). Other factors (smoking status, ethnicity, geographical location) could influence the relationship between ICS effect and blood eosinophil count, but remains to be further explored. The mechanism for an increased ICS effect in COPD patients with higher blood eosinophil counts remains unclear. There is insufficient evidence to recommend that blood eosinophils should be used to predict future exacerbation risk on an individual basis in COPD patients.[1]

The problem in Indonesia regarding inhalation therapy in COPD patients is the high price of inhalation drugs. Although that has been helped by the national health insurance system, for LAMA inhalation is still relatively expensive, therefore the regulation of its administration is very difficult. Based on the GOLD COPD 2019 therapy algorithm, LAMA is the first choice in COPD group C and D therapy. While the administration of LABA + ICS therapy is only in COPD group D by considering blood eosinophil count.

CONCLUSION

This study may provide information and characteristic of COPD patient in Indonesia rural area and showed who may have benefit to ICS therapy based on recommendation GOLD COPD 2019. Blood eosinophils counts is a low-cost biomarker and may help clinicians to made decision therapy.

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ORIGINAL ARTICLE

Analysis of Vitamin D Levels on Bronchiectasis Severity

Yacob Arawamin Batkunde[1], Muhammad Ilyas[1,2], Irawaty Djaharuddin[1], Nur Ahmad Tabri[1,2], Harun Iskandar[1,2], Arif Santoso[1]

[1]Departement Pulmonology and Respiratory Medicine Faculty of Medicine, Hasanuddin University/ Wahidin Sudirohusodo Hospital, Makassar
[2] Departement Pulmonology and Respiratory Medicine Faculty of Medicine, Hasanuddin University, Makassar

ABSTRACT

Background: Bronchiectasis is a chronic disease caused by repeated infection and inflammation of the bronchial walls. Vitamin D plays a role secretion of antimicrobial peptide and inhibits release of pro-inflammatory cytokines in the lungs. Vitamin D deficiency is associated with exacerbations, severity and decreased lung function in bronchiectasis. Several studies have found an association between vitamin D levels and bronchiectasis severity.

Method: This study used cross-sectional study design with consecutive sampling method on bronchiectasis patients who enrolled outpatient and inpatient at Wahidin Sudirohusodo hospital in February - May 2020. All research procedures obtained the approval of the Health Research Ethics Commission, Medicine faculty, Hasanuddin University Makassar. Bronchiectasis severity was assessed based on the FACED score (FEV_1, Aged, chronic Colonization by Pseudomonas aeuroginosa, radiological Extension of the disease, Dyspnea). Levels of vitamin D serum (25OHD) were measured using the ELISA method.

Results: The study subjects were 44 patients, consisting of 61.4% male and 38.6% female. Most of the bronchiectasis patients in this study were mild (77.3%) based on the FACED score, 15.9% moderate and 6.8% severe. As many as 77.3% of patients had vitamin D deficiency and insufficiency as much as 9.1%. All patients with moderate-severe FACED scores had vitamin D deficiency. The correlation between vitamin D levels and FACED scores showed a positive significant.

Conclusion: There is a positive correlation between low vitamin D levels and the severity of bronchiectasis (P=0.04)

Keywords: bronchiectasis, vitamin D, FACED score, severity

*Correspondence: Yacob Arawamin Batkunde - yacobbatkunde@gmail.com

Submitted: February 4th 2021, Accepted: February 11th 2021, Published: February 28th 2021

INTRODUCTION

Bronchiectasis is a chronic disease with high morbidity. Abnormal airway dilatation in bronchiectasis causes impaired mucociliary clearance that leads to mucus buildup, recurrent infection and inflammation. The clinical symptoms of bronchiectasis are similar to those of other lung diseases and require additional radiological examination using high resolution computed tomography scan (HRCT) thorax.[1–3] The parameters to assess the severity of bronchiectasis were included in bronchiectasis severity index (BSI) or FACED (Forced expiratory volume in one second/FEV_1, Aged, Chronic colonization by *Pseudomonas aeuroginosa*, radiological Extension of the disease, Dyspnea) scoring systems.[4–6]

Vitamin D plays a role in suppressing inflammation and regulating antimicrobial peptide secretion in respiratory system. Enzyme 1α-hydroxylase plays a role in the activation of vitamin D expressed by airway epithelium, alveolar macrophages, dendritic cells and lymphocytes.[7–9] Vitamin D deficiency is often associated with high colonization, exacerbations and severity rates of bronchiectasis. Vitamin D deficiency can occur due to insufficient sunlight exposure and nutrient intake, liver disease, kidney disease and loss of vitamin D binding protein.[8–10]

Vitamin D deficiency is often associated with high colonization, exacerbations and severity rates of bronchiectasis.[10] Vitamin D deficiency can occur due to insufficient sunlight exposure and nutrient intake, liver disease, kidney disease and loss of vitamin D binding protein.[8,9.]

Several studies have found a correlation between vitamin D levels and bronchiectasis. As for the studies in Indonesia regarding the correlation between vitamin D levels and respiratory diseases including bronchiectasis are still limited. This is the author's background for the to research the effect of vitamin D on the severity of bronchiectasis.

METHOD

A cross-sectional study was conducted. This study was performed in the department of pulmonology and respiratory medicine of Wahidin Sudirohusodo General Hospital and included 44 subjects that met the inclusion criteria. Written and verbal informed consent was obtained from every participants according to approval of the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University No: 191/UN4.6.4.5.31/PP36/2020.

The inclusion criteria for this study is a male or female HRCT confirmed bronchiectasis patients ≥18 years of age and able to complete spirometry test. The severity of bronchiectasis was assessed based on FACED score (FEV1, Aged, chronic Colonization by *Pseudomonas aeuroginosa*, radiological Extension of the disease, Dyspnea). Vitamin D (25OHD) serum levels was measured using the ELISA method. The exclusion criteria were bronchiectasis patients with incomplete examination results.

Statistical analyses were completed using the SPSS statistical software package (version 24.0). The obtained results will be displayed in a narrative equipped with tables and graphs.

RESULT

A total of 44 subjects consisting of 27 men (61.4%) and 17 women (38.6%) with the largest proportion of age ranging from 50 to 59 years old (31.8%). Microbial culture showed colonization in 20 patients (45.4%), i.e. *Acinetobacter baumanii* (6.8%), *Klebsiella pneumonia* (6.8%), and *Pseudomonas aeruginosa* (4.5%). Lung lesion extension were based on the number of affected lobes, 34 patients with ≤2 affected lobes (77.3%) and 10 patients with >2 lobes of (22.7%).

Table 1. Characteristics of The Participants

Variables	N	%
Sex		
Male	27	61.4
Female	17	38.6
Age (years)		
18-29	3	6.8
30-39	7	15.9
40-49	6	13.6
50-59	14	31.8
60-69	9	20.5
≥ 70	5	11.4
Body Mass Index (BMI)		
Underweight	16	36.4
Normal	16	36.4
Overweight	12	27.3
FEV_1/FEV_1 (%)		
≥50%	24	54.5
<50%	20	45.5

Table 1. Characteristics of The Participants (cont.)

Variables	N	%
Colonization		
None	24	54.5
Acinetobacter baumanii	3	6.8
Klebsiella pneumonia	3	6.8
Pseudomonas aeruginosa	2	4.5
Other microorganisms	12	27.3
Lung lesion extension (affected lobes)		
≤2	34	77.3
>2	10	22.7
mMRC		
≤2	29	65.9
>2	15	34.1
FACED Score		
Mild	34	77.3
Moderate	7	15.9
Severe	3	6.8
Vitamin D		
Normal (≥ 30 ng/ml)	6	13.6
Insufficiency (10-<30 ng/ml)	4	9.1
Deficiency (<10 ng/ml)	34	77.3

Table 2. The Relationship Between Characteristics and Vitamin D Levels

Characteristics	Vitamin D Levels			Total	P
	Deficiency	Insufficiency	Normal		
Sex					
Male	19(55.9%)	3 (75%)	5(83.3%)	27 (61.4%)	0.016
Female	15(44.1%)	1 (25%)	1(16.7%)	17 (38.6%)	
Body Mass Index (BMI)					
Underweight	10(29.4%)	2 (50%)	4(66.7%)	16 (36.4%)	
Normal	13(38.2%)	1 (25%)	2(33.3%)	16 (36.4%)	0.010
Overweight	11(32.4%)	1 (25%)	0 (0.0%)	12 (27.3%)	
FEV_1					
<50%	17 (50%)	0 (0.0%)4	3 (50%)	20 (45.5%)	0.923
≥50%	17 (50%)	(100%)	3 (50%)	24 (54.5%)	
Age (years)					
<70	30(88.2%)	3 (75%)	6 (100%)	39(88.6%)	0.853
≥70	4 (11.8%)	1 (25%)	0 (0.0%)	5 (11.4%)	
Colonization					
None	32 94.1%)	4 (100%)	6 (100%)	42 (95.5%)	0.420
P. aeruginosa	2 (5.9%)	0 (0.0%)	0 (0.0%)	2 (4.5%)	

Table 2. The Relationship Between Characteristics and Vitamin D Levels (cont.)

Characteristics	Vitamin D Levels			Total	P
	Deficiency	Insufficiency	Normal		
Lung lesion extension					
≤2 lobes	25 73.5%)	3 (75%)	6 (100%)	34 (77.3%)	0.268
>2 lobes	9 (26.5%)	1 (25%)	0 (0.0%)	10 (22.7%)	
mMRC					
≤2	23(67.6%)	3 (75%)	3 (50%)	29 (65.9%)	0.442
>2	11(32.4%)	1 (25%)	3 (50%)	15 (34.1%)	

Table 3. The Relationship Between Bronchiectasis Severity Based On FACED Score and Vitamin D Levels

FACED Score	Vitamin D Levels			Total	P
	Deficiency	Insufficiency	Normal		
Mild	24 (70.6%)	4 (100%)	6 (100%)	34 (77.3%)	0.04
Moderate-Severe	10 (30.4%)	0 (0.0%)	0 (0.0%)	10 (22.7%)	

The severity of the disease was classified based on the FACED score, mild bronchiectasis was found in 34 patients (77.3%), moderate bronchiectasis was found in 7 patients (15.9%), and severe bronchiectasis in 3 patients (6.8%). In blood serum examination, normal vitamin D levels was found in 6 patients (13.6%), insufficiency in 4 patients (9.1%), and deficiency in 34 patients (77.3%). The data is illustrated on table 1 below.

Table 2 depicts the relationship between characteristics of the study participants and vitamin D levels. We found statistically significant relationships between vitamin D levels and both sex and nutritional status in bronchiectasis patients ($P<0.05$). It indicates that vitamin D levels in women were lower than in men. In addition, higher rates of normal and insufficient vitamin D levels were found in patients with lower BMI than those with normal BMI.

Based on Table 2 also showed no significant association between vitamin D levels and the parameters of the FACED score (FEV_1, age, colonization, lesion area and mMRC score) with $P>0.05$. It means that the level of vitamin D statistically has no positive or negative correlation with the FACED score parameters.

Table 3 showed that in 44 subjects, we found that all patients with moderate-severe FACED scores had vitamin D deficiency. The association between vitamin D levels and FACED scores in bronchiectasis patients was assessed by a non-parametric test that resulted in $P=0.04$, which means that there is a significant positive

relationship between vitamin D levels and FACED score.

DISCUSSION

Fourty four patients with bronchiectasis were included in the study. Twenty seven were male (61.4%) and 17 were female (38.6%). This is consistent with a study by Bhatta et al which found that the incidence of bronchiectasis was more in men than women, 70% and 30% respectively.[11] Several studies found different results, Habesoglu et al and Martınez-Garcıa et al reported higher incidence in women compared to men.[12,13]

The different results found in each sex can be caused by several factors, including the higher number of smokers in men, exposure to other harmful gases or particles, differences in the structure of respiratory tract, microbial composition and function.[5,14] Higher smoking rates in men in several Asian countries including Indonesia may be associated with a higher incidence of bronchiectasis in men than women.[11,15]

This study reported the highest incidence of bronchiectasis in 50-59 years age group (31.8%). Several studies had also shown that the incidence rate is the highest in the same age range.[12] The incidence of bronchiectasis increased substantially with increasing age. The increasing prevalence of bronchiectasis in the older age group is associated with longer and higher exposure to dust/ harmful particles.[16]

This study did not find any statistically significant relationship between vitamin D levels and FEV_1. It may occured because the FEV_1 examination was not carried out regularly, making it difficult to evaluate the relationship between vitamin D levels and the decrease in FEV_1. Studies by Ilyas et al and Malinovschi et al also did not find any significant relationship between vitamin D levels and the degree of obstruction (FEV_1).[17,18] A study by Chalmers et al found a greater decrease in FEV_1 in bronchiectasis patients with vitamin D deficiency compared to the normal group because the study assessed FEV_1 over 3 years of observation. Several studies also found a significant correlation after several years of observation.[10]

Microbial culture reported colonization occurred in 20 patients (45.4%), i.e. *Acinetobacter baumanii* and *Klebsiella pneumonia* 6.8% each, and *Pseudomonas aeruginosa* 4.5%. It is similar with studies by Bhatta et al and Bopaka et al which reported low colonization of microorganisms, 50% and 35% respectively. Colonization easily occurs due to permanent

changes in airway structures, impaired mucociliary clearance, increased mucus viscosity and repeated exposure to harmful gases/ particles. In addition, a history of antibiotics use in the previous health facility may contribute to negative culture.[19–21] In this study, it could be possible that there was a history of antibiotics administration from the previous hospital, leading to many negative culture results.

The proportion of vitamin D levels was found to be 77.3% for deficiency, 13.6% for normal level and 9.1% for insufficiency. This study is somewhat different from several studies in Indonesia. Studies by Suryadinata et al and Widyaswari et al found high rates of vitamin D deficiency and insufficiency.[22,23] A study by Saragih JP et al on tuberculosis (TB) patients in Medan found a high rate of vitamin D insufficiency, but did not find which patients had vitamin D deficiency.[24] Other studies have shown a low vitamin D concentrations in the population in Indonesia even though they get enough sunlight exposure. It showed that there are various factors that affect vitamin D levels, especially as the dietary sources are limited.[22]

FACED score is an instrument to evaluate the severity and prognosis of bronchiectasis through an analysis of five parameters. FACED score was developed specifically to predict mortality rate within five years after treatment for various etiologies, thus providing a rapid assessment of bronchiectasis severity in the early stage of the disease.[6] According to the FACED score, we found that 34 patients had mild bronchiectasis (77.3%) and 10 patients had moderate-severe bronchiectasis (22.3%). The number of patients with moderate-severe category in this study was less due to the lack of subjects with high score parameters, such as age of ≥70 years and FEV_1 ≤50%, thus affecting the final score of FACED.

In this study, we reported that all patients with moderate-severe FACED scores were accompanied by vitamin D deficiency. This study showed a statistically significant relationship between vitamin D levels and FACED scores (P=0.04). Vitamin D deficiency is one of the risk factors that aggravate bronchiectasis because it may increase the inflammatory response and susceptibility to recurrent infections in the lungs. Vitamin D deficiency that accompanies bronchiectasis is often caused by lack of sunlight exposure and nutrient intake.[10,25] Therefore, vitamin D levels evaluation can be considered as an indicator of the inflammatory response and the severity of bronchiectasis.[25,26] Several studies had

also demonstrated the benefit of vitamin D supplementation for patients with bronchiectasis, asthma, chronic obstructive pulmonary disease (COPD) and pulmonary tuberculosis.[25]

A study by Ferri et al., assessing the association of vitamin D with bronchiectasis severity using BSI scoring system, had found a statistically significant association between vitamin D levels and BSI scores. This study also found that low vitamin D levels were associated with the disease clinical and radiological severity score.[10,26] Several studies used a parameter of inflammatory marker in bronchiectasis patients and showed a significant correlation between the two.[26]

The limitation of this study is that not all radiological examination results include the type of bronchiectasis and do not use the Reiff or Bhalla score which serves more detailed description about bronchiectasis lesions. It is important to determine the type of bronchiectasis in assessing the severity of BE. In addition, it is also used to determine Reiff or Bhalla scores. The higher the score, the more severe the radiological severity of bronchiectasis. Therefore, researchers only analyzed vitamin D levels against the number of lobes affected. If further analysis was carried out between vitamin D levels and the severity of bronchiectasis based on reiff or Bhalla scores, it was possible to find a significant association.

CONCLUSION

There is a positive correlation between low vitamin D levels and the severity of bronchiectasis.

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ORIGINAL ARTICLE

Proportion of Pneumoconiosis In Limestone Mining Workers In Citatah Village, West Bandung District

Widhy Yudistira Nalapraya[1], Agus Dwi Susanto[2], Mukhtar Ikhsan[2], Muchtarrudin Mansyur[3], Caecilia Marliana[4]

[1]Faculty of Medicine, Bandung Islamic University
[2]Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Indonesia/ Persahabatan Hospital, Jakarta
[3]Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta
[4]Faculty of Medicine, Trisakti University, Jakarta

ABSTRACT

Background: Silica, asbestos, and coal dusts correlate with pneumoconiosis in mineworkers. The International Labor Organization (ILO) reported that 30-50% of workers in developing countries were diagnosed with pneumoconiosis. This study aimed to identify pneumoconiosis among limestone workers in Indonesia.

Method: This cross-sectional study involved 73 limestone mineworkers from two limestone mining sites in Citatah Village, West Bandung Regency, Indonesia, as the subjects. Two out of three AIR-Pneumo-certified blinded readers decided the conclusive chest x-ray (CXR) report of pneumoconiosis for each subject according to the ILO guidelines.

Results: Pneumoconiosis was found in 11/73 (15.1%) subjects. The median age of pneumoconiosis group was older compared to the non-pneumoconiosis group (51 [33-63] vs. 37.5 [18-85] years old, P=0.013). All subjects in the pneumoconiosis group were of> 6 years of working duration (P=0.001). The dust concentration was higher at the mining site of the pneumoconiosis group compared to the mining site of the non-pneumoconiosis group (61.41±103.98 vs. 14.92±55.17 mg/m^3, P=0.030). This study showed that working duration and mining site dust concentration were risk factors for pneumoconiosis; however, with no significance (OR=14.6, P=0.999 and OR=7,171, P=0.998, respectively).

Conclusion: The proportion of pneumoconiosis in limestone mine workers in this study was 15.1%. Working duration and mining site dust concentration were risk factors for pneumoconiosis; however, no significance was found from this study.

Keywords: pneumoconiosis risk factor, mining site dust, mining working duration, limestone mineworkers

*Correspondence: Widhy Yudistira Nalapraya - arijulian94@gmail.com

Submitted: January 13th 2021, Accepted: February 9th 2021, Published: February 28th 2021

INTRODUCTION

In the current era of industrialization, there has been an increase in industrial activity involving various other sectors such as mining. Mining workers are a vulnerable population that can contract occupational lung disease, one of which is pneumoconiosis. Data released by the World Health Organization (WHO) in 1999 showed that there were 1 million deaths among workers, 5% of which were caused by pneumoconiosis. Data from the International Labor Organization (ILO) in 2013 shows that as many as 30-50% of workers in developing countries, one of them is Indonesia, experience pneumoconiosis.[1]

This fact is also supported by the results of research conducted at the University of Indonesia with a cross-sectional study approach in 51 miners. The results of the study stated that there were 9.8% (5 people) experienced pneumoconiosis among mining workers. The level of dust in the mining work environment also has a much higher number than the safe limit of 10 mg/m^3, which is 2.09347-22.4887 mg/m^3.[2]

Pneumoconiosis is a disorder that occurs due to the accumulation of dust in the lungs which causes a tissue reaction to the dust, the main reaction due to dust exposure is fibrosis.[2,3] Pneumoconiosis is caused by inhalation of dust which mostly comes from mining and agriculture. Globally, there are three types of mining dust that often cause pneumoconiosis, namely silica, asbestos and coal.[3] Pneumoconiosis caused by chronic exposure to silica is known as silicosis. Apart from being found in mining areas, silica dust is also found in areas of sand blasting, stone cutting and quarrying.[3,4] Silicosis is known to manifest in pulmonary fibrosis which can progress even after the exposure is stopped.[5]

METHOD

This research is a cross sectional study. Limestone mining workers in Citatah Village, West Bandung Regency who meet the inclusion and exclusion criteria. The sample size uses the Slovin formula because the prevalence of pneumoconiosis in West Bandung Regency is not yet known, the total sample size is added by 10% of the calculation of the sample size as a reserve so that the sample size becomes 90 subjects.

The inclusion criteria were limestone miner and willing to participate in research with signed an informed consent. The exclusion criteria were had chronic lung disease

(asthma, COPD, pulmonary tuberculosis) and a history of thoracic surgery before the worker worked in the mine.

Chest photo interpretation required for doctors who read thoracic photos based on NIOSH guidelines, namely that they already have an ILO certificate who is trained and experienced including interpreting chest photos and demonstrating competence in reading chest photos of pneumoconiosis for NIOSH B certificate qualifications and or nationally certified as a pulmonologist, radiologist, and occupational medicine.[6] The reading of the ILO chest photo was carried out independently by two people, namely a pulmonary doctor and an occupational medical doctor who had an ILO certificate. Conclusions are drawn from the same two experiments.

The results of the ILO chest X-ray interpreted yes for a positive chest radiograph for pneumoconiosis and no for a chest X-ray for no pneumoconiosis. For the interpretation of shape and size, if two interpretations mention the regular small opacity form for any size between p, q and r, it is concluded that the parenchymal abnormality of regular small opacity, the same applies to irregular small opacity and large opacity. For the density level, if two interpretations read the density between 1 / 0.1 / 1 / 1/2 it is concluded that the density is 1, if there are no two interpretations in a certain density level then it is written as descriptive.

RESULT

This study describes the main parameters namely therapeutic data and blood eosinophils in COPD patients, as well as several characteristics. These characteristics include gender, age, education, Brinkman index, duration of diagnosis, nutritional status (BMI), degree classification based on GOLD, and COPD group. There are 57 patients has been assessment. The characteristics of research subjects can be seen in Table 1.

This study is a cross-sectional test to determine the proportion of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency by using a screening questionnaire for chronic respiratory diseases, chest X-ray based on ILO guidelines and pulmonary function tests. The results of the chest photo were read by 2 readers from pulmonary doctors and occupational doctors. If there is a difference in the reading by the third reader, namely the radiology doctor, the conclusion drawn is the result of reading the two photos with

the same conclusion. Citatah village has 5 companies that have limestone mines with a total population of 100 workers. The first thing to do in the research is to ask the company permission to conduct research from 5 companies, only 2 companies that give permission.

Table 1. General characteristics of limestone mining workers in Citatah Village, West Bandung Regency.

	Pneumoconiosis		**Not pneumoconiosis**	
	N	**%**	**N**	**%**
Limestone miner	11	15.1	62	84.9

Table 2. Characteristics of subjects based on pneumoconiosis

Variable	**Pneumoconiosis**		**Not pneumoconiosis**		**P**
	N	**%**	**N**	**%**	
Age*	51	33-63	37.5	18-85	0.013 (b)
Gender					
Male	11	100	54	87.1	0.598 (d)
Women	0	0	8	29.9	
Educational status					
Junior High School	5	45.5	42	67.8	
Middle High School	4	36.4	11	17.7	0.210 (C)
High school	2	18.1	9	14.5	
Working time					
<8 hours	1	9,1	14	22.6	0.441 (d)
≥8 hours	10	90.9	48	77.4	
Smoking habit					
Smoker	10	90.9	41	66.1	
Former smoker	0	0	1	1.6	0.100 (c)
Not a smoker	1	9,1	20	32.3	
Body Mass Index (BMI)					
Less	0	0	4	6.5	
Normal	8	72.7	42	67.7	0.734 (c)
More	3	27.3	14	22.6	
Obesity	0	0	2	3,2	
Length of working					
<6 years	0	0	37	59.7	
6-10 years	8	72.7	17	27.4	0.001 (c)
> 10 years	3	27.3	8	12.9	
Use of PPE					
Yes	2	18.2	15	24.2	1,000 (d)
Not	9	81.8	47	75.8	

Table 2. Characteristics of subjects based on pneumoconiosis (cont.)

Variable	Pneumoconiosis		Not pneumoconiosis		P
	Median	Min-Max	Median	Min-Max	
Interpretation of pulmonary function disorders					
Failed to maneuver	1	9	5	8.1	
Normal	5	45.5	44	71	
Restriction	3	27.3	5	8.1	0.222 (c)
Obstruction	2	18.2	7	11.3	
Mix	0	0	1	1.5	
Company dust level 1* (mg/m^3)	0.6966	0.6966-0.6966	0.6966	0.6966-0.6966	1.000 (b)
Company dust level 2* (mg/m^3)	223.3	0	40.78	88.1	0.002 (a)
Dust level at 2 companies*	61.41	103.98	14.92	55.27	0.030 (a)
Work location					
Limestone mine	8	72.7	58	93.5	0.065 (d)
Limestone mill	3	27.3	4	6.5	

Note: (*) Mean value (standard deviation) for normal distribution; median (minimum-maximum) value for abnormal distribution; (%) Percentage of total sample (N = 73); (a) Unpaired T-test with the same variance; (b) Mann-whitney test; (c) Kendall's-tau; (d) Fisher's Test.

Table 3. Description of International Labor Organization chest X-ray abnormalities

ILO classification	Reader 1	Reader 2	Reader 3
Parenchymal abnormalities consistent with pneumoconiosis			
shape	6	0	6
P	3	0	2
Q	1	-	2
R	1	-	1
S	1	-	1
T	-	-	-
U	-	-	-
Profusion			
0/0	-	-	-
0/1	5	-	2
1/0	-	-	1
1/1	1	-	1
½	-	-	-
2/1	-	-	1
2/2	-	-	-
2/3	-	-	1
Pleural abnormalities consistent with pneumoconiosis	5	0	5
Costophrenic angle obliteration	5	0	5

The first company works only to take limestone with a total of 50 workers, the second company works taking limestone and then grinding limestone into lime flour has 30 workers. 80 workers were screened with a respiration questionnaire. Here, 5 people were excluded because 2 people had a history of chest injuries and 3 people had a history of pulmonary tuberculosis treatment while 2 more people refused to become the study subjects.

The total number of workers who met the study inclusion criteria was 73 people. Workers who met the inclusion criteria and were willing to take part in the study were subjected to a chest X-ray of the ILO criteria and spirometry as many as 73 people, 73 thoracic photos are read by two readers independently, both readers do not know the results of the interpretation of one photo from another, there are 11 photos that have different interpretations from 2 readers then 11 photos are read by a third reader who is still carried out independently. according to NIOSH guidelines.

Out of a total of 73 workers, 11 people (15.1%) had ILO chest radiographs according to pneumoconiosis. There were 5 people with parenchyma abnormalities with regular small opaque form, one small irregular opaque disorder measuring about 1.5 mm. The density level of 2 people with a density of 0.1 people with a density of 1, the other 3 people density is described in Table 3. Five subjects had pleural abnormalities that were compatible with pneumoconiosis and costoprenic obliteration.

Of the total subjects, the median age was 42 (range 18-85). Subject The majority of men were 65 people (89%). The majority of education levels are SD graduates as many as 47 people (64.4%). Time worked ≥8 hours as many as 58 subjects (79.5) The majority of subjects were smokers as many as 51 people (69.9%). The body mass index of the majority of the subjects was normal as many as 50 people (68.5%). The majority of the subjects <6 years old were 37 people (50.7%). The majority of subjects did not use PPE as many as 56 people (76.7%).

Pulmonary physiology examination of the subjects median CVD 3300 ml (1310-4570 ml), %KV median 97.8% (65.1-168%), median CVP 3270 ml (1200-4500 ml), %FVC median 96.2% (64-164%), median FEV_1 2680 ml (910-3840 ml), $\%FEV_1$ median 95% (39.3-173%) and median $\%FEV_1/FVC$ 83.2% (42.5-96.9%). Pulmonary function disorders, the majority of obstruction disorders, were

9 people (12.3%).

DISCUSSION

According to the International Labor Organization (ILO) pneumoconiosis is a non-neoplastic disorder that occurs due to the accumulation of dust in the lungs which results in finger reactions, especially fibrosis reactions.[7,8] The oldest type of pneumoconiosis is known as silicosis, which is a diffuse interstitial fibronodular lung disease caused by inhalation of crystalline silica, one of which is often found in limestone mining workers.[8]

In this study, there were 11 out of 73 people (15.1%) workers of limestone miners with ILO chest X-rays according to pneumoconiosis. The proportion of limestone mining worker pneumoconiosis in Citatah Village, West Bandung Regency is higher than in several other studies in Indonesia, research by Pandu et al. in 2005 in a steel knife factory in 2002 found 5% of radiological images suspected of pneumoconiosis, Bangun et al's research in 2017 on stone mining workers at PT. A in Bandung found 9.8% pneumoconiosis and research by Damayanti et al. in 2007 on cement factories also found 4.9% cases of pneumoconiosis from chest X-ray examination.[2,7,9]

Research data in the United Kindgom, there has been a decrease in the incidence of silicosis and CWP in the last 10 years. There were 30 new cases of silicosis in 2017 reported by the Industrial Injuries Disablement Benefit (IIDB), compared to 85 in 2008 with the discovery of new silicosis cases. Research in China, pneumoconiosis is classified into 13 categories, namely; silicosis, coal workers Pneumoconiosis (CWP), graphite pneumoconiosis, and others. In 2008 to 2013, there were 3,665 cases of pneumoconiosis (85.61% of all occupational diseases) reported in Hubei province.[10]

Other studies in China stated that more than 70% of pneumoconiosis cases were silicosis cases in the cities of Wuxi, Yancheng, and Suzhou. This may be related to population size and industrial structure, and the type of economy in the ability to prevent and control occupational diseases.[11]

Centers for Disease Control and Prevention (CDC) in 2012 stated that there were 7% cases of pneumoconiosis from 2005-2009 based on radiographs from workers with 25 years of exposure.[12] The incidence of pneumoconiosis in some developed countries has decreased. This is because there are disease prevention

programs recommended by legal institutions, including ventilation systems, sprinklers and dust capture devices. In several industries, the use of masks as protection has been promoted. Periodic examinations, such as spirometry and radiographs on workers are carried out every 5 years.[11,12]

Physiological disorders of the lungs and respiratory tract in labour, including in limestone mining workers, can be influenced by internal (from within humans) and external (from outside humans).[13]

The analysis conducted in this study showed that there was a relationship between age and the incidence of pneumoconiosis in limestone miners in Citatah Village, West Bandung Regency in 2018 with P=0.013. This is consistent with research conducted by Isara et al. (2016) on 113 mining workers consisting of 76 field workers as cases and 37 office workers as controls in Edo State, Nigeria with P=0.01 workers who have respiratory symptoms in workers. mines exposed to dust compared to workers who were not exposed had an age of 42±12.7 years versus 36.2±10.6.[14]

This is also supported by the research of Tolinggi et al. (2015) with a value of P=0.005 which compared serum IL-8 levels and pulmonary function in 9 limestone mining industry workers in Wangun Village, Palang District, Tuban Regency as a case with 9 workers in the Semanding District office as a control. Mining workers carry out activities such as excavating, crushing, and cutting limestone without the use of PPE.[15] The pathogenesis of pneumoconiosis is determined by two main factors, namely dust particles in the form of concentration and particle size (<5μm) and individual vulnerability in the form of body response, especially the airway to particles the dust.[14,16]

Age factor affects the vulnerability of the body, physical condition and lung function capacity. Pulmonary function capacity will continue to increase to a maximum point at the age of 19 to 21 years and then decrease with age. At the age of 30 years, the average lung capacity is 3000-3500 ml while at the age of 50 years it decreases to less than 3000 ml. Other than that, older age had a higher sensitivity to COPD and the cumulative total dust exposure. This condition will be exacerbated by a dusty environment and other factors such as smoking habits and diseases related to the respiratory tract.[17,18]

Research conducted by Apsari et al. (2018) showed insignificant results on the relationship between age and occupational lung disease in 31 sand

and stone mining workers in Rowosari Village, Semarang City in 2017 (P=1.000). This difference may be due to this study using a numerical scale for age, whereas Apsari et al. (2018) made age into a nominal scale by dividing the age group into two, namely the age group >30 years and ≤30 years. At the age of 30 years, lung capacity has decreased, but the respiratory muscle function will significantly decrease about 20% at the age of 40 years.[19]

Based on the results relationship between length of work and the incidence of pneumoconiosis in workers in a limestone mine in Citatah Village, West Bandung Regency in 2018 (P=0.001). This is in line with the theory and research conducted by Budiono (2007) and Simanjuntak et al. (2015) who stated that the length of work had a significant relationship with the incidence of pneumoconiosis, related to the cumulative dose of dust particles in the lungs. The composition of limestone consists of 95% $CaCO_3$, 11% $MgCO_3$, and 1 - 20% crystalline silica which, if exposed for a long period of time and with a weight of 2-5 mg/m^3 caused an inflammatory reaction.[17,20] A multivariate analysis of length of work with pneumoconiosis was performed OR=14.639 and P=0.989. It is concluded that the longer working in this study is divided into >10 years has a 14.639 times risk of developing pneumoconiosis compared to mining workers who work <6 years although it is not statistically significant.

In contrast to this study which divided the sample into three categories, namely, length of work <6 years, 6-10 years and> 10 years, Budiono (2007) and Simanjuntak et al (2015) only divided the sample into two, namely, length of work <10 years and ≥10 years. Splitting the division into 3 (three) groups was carried out to reduce bias due to the uneven distribution with the number of samples with a length of service> 10 years of only 12.32%.[17,20] This can be caused by individual susceptibility factors and a history of dust exposure in previous places not studied and is a limitation of this study.[21]

The results of the variable analysis of dust levels on pneumoconiosis in the study in company 2 with P=0.002, versus P=1.000 in company 1. Research by Simajuntak et al divides dust levels into high (> 3 mg/m^3) and low (≤3 mg/m^3). Of the total subjects with high dust levels of 28 people, 18 subjects (64.3%) had chest X-ray images of pneumoconiosis, while 10 subjects who did not have chest X-ray images of pneumoconiosis (35.7%). Meanwhile, from a total of 10 subjects with low dust levels, there are 2

subjects (20%) had chest X-ray images of pneumoconiosis while 8 subjects (80%) had no features of pneumoconiosis. The results of the analysis of the relationship between dust levels and the incidence of pneumoconiosis obtained a significance value of P=0.027.

Besides, Tse LA, et al (2015) conducted a retrospective cohort study of 3,492 workers exposed to silica from iron ore, with a monitoring time of 33 years. This study developed a risk scoring system using a linear combination of predictor values by LASSO. Six predictors were selected into the final prediction model; age at entry, mean concentration of inhaled silica, years of exposure, smoking, illiteracy, and number of jobs. In this study, the mean predictors of inhaled silica dust were divided into <0.05 mg / m3 (coefficient value 0 and HR 1.00), 0.05-0.10 mg/m^3 (coefficient value 2.14 and HR. 8.52 (95% CI 3.96-18.33)), 0.10-0.15 mg / m3 (coefficient value 3.41 and HR=30.28 (95% CI=14.08-65.13), and ≥0.15 mg/m^3 (coefficient value 4.23 and HR=68.64 (95% CI=31.83-147.98) with P<0.001).[22]

Buchanan D, et al. (2003) who conducted monitoring on 547 workers. For workers who aged 50-74 years, the logistic regression model is calculated by dividing the two time periods. In the period before 1964, the OR for the 2/1+ risk was 0.995 (95% CI=0.977-1.014) and the post 1964 OR for 2/1+ was 1.811 (1.536-2.136). The calculation of the risk of silicosis must take into account the intensity of quartz exposure, particularly at concentrations of 1 or 2 mg / m3, even though the exposure time period is brief.[23]

In this study, the cumulative quartz exposure group was divided into <2 mg/m^3 and ≥2 mg/m^3. Even though these two exposures are in the same unit, the coefficient at the higher dust concentration is tripled. The calculation model used in this study predicts a silicosis risk of 2.5% over 15 years of 0.1 mg/m^3 dust exposure. which increased to 10.6% with the addition of only four months of exposure to a concentration of 2 mg/m^3, and to 72% annually at higher exposures. Estimated exposure of 1 g.h/m^3 at concentrations> 2 mg/m^3 corresponds to the predicted risk of a radiographic abnormality of about 3 g.h/m^3. This study did not detect the effect of time of exposure.[23]

Based on the analysis of the results of the research conducted, it was found that P=0.598 showed that gender was not related to the incidence of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency in 2018. This is

supported by research conducted by Isara et al. (2016) with results P=0.59, Blackley et al. (2014) with P=0.44 and Yen et al. (2015) with P=0.99.[14,24,25] In contrast to this study, research by Brass et al. (2010) proved that there was a significant relationship between female and male sex in miceC57BL/6 (P<0.005) by attributing the expression of Esterogen Receptor alpha (ER-α) to the incidence of silicosis in mice induced intratracheal silica crystalline 0.2 g/kg.[26]

Esterogens can induce TNF-α production in macrophages and increase macrophage-specific chemokines in fibrosis and lung tissue inflammation.[27] Macrophages are a cellular immune system that clears small particles by means of phagocytosis, TNF-α is an indicator of the prognosis of pneumoconiosis. Furthermore, in response to TNF-α and IL-1, IL-8 will act as chemokines released by various cell types including fibroblasts, then activate and call neutrophils which in turn induce the inflammatory process.[26]

The results of the analysis in this study showed that nutritional status related to the incidence of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency in 2018 (P=0.734). This is supported by research conducted by Zheng et al. (2017) with P=0.134.[28]

The results of the analysis in this study indicate that there is no significant relationship between educational status and the incidence of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency in 2018 (P=0.210), according to the research conducted by Isara et al. (2016) on 113 mining workers consisting of 76 field workers as cases and 37 office workers as controls in Edo State, Nigeria with a result of P=0.25.[14] However, research conducted by Ayaaba et al. (2017) on 1001 male workers in Obuasi and Tarkwa from December 2015 to April 2016 showed significant results (P<0.001).[29]

The results of the analysis in this study indicate that there is no relationship between working time and the incidence of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency in 2018 (P=0.441) because in this study the majority of workers worked more than 8 hours, namely 58 workers (79.5%) so it is difficult to describe the relationship between working time and pneumoconiosis. This result is supported by research conducted by Budiono et al. (2007).[17] The results of this study are inconsistent with the

theory of increased risk of exposure and incidence of occupational diseases during longer working hours.[30]

The results of the analysis in this study showed that there was relationship between smoking habits and the incidence of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency in 2018 (P=0.100). This is supported by research conducted by Budiono (2007)[17] and Isara et al. (2016).[17] Which is also in line with the research by Tolinggi et al. (2015) on workers in the limestone mining industry in Wangun Village also supports the results of this study with a value of P=0.885 despite the different scale variables in the research of Tolinggi et al. (2015) used a numerical scale for the number of cigarettes per day, while this study used an ordinal scale which divided the sample into three groups, namely smokers, former smokers and non-smokers.[15] Research conducted by Apsari et al. (2018) also did not show a significant relationship between smoking habits and the incidence of lung disease due to work on 31 sand and stone mining workers (P=0.139).[19]This indicates that smoking habits are not a major factor in the incidence of pneumoconiosis.

Chemical substances in cigarettes such as nicotine, tar, CO, and nitrosamine can damage the cilia hairs in the airways which function as a filter for air that enters breathing and activate alveolar macrophages and inflammatory cells which in turn induce chronic inflammation of the airway, lung parenchyma, and pulmonary vessels.[28,30,31]

Based on the analysis of the relationship between the use of PPE and the incidence of pneumoconiosis, the p value is 1,000. This result is supported by research conducted by Pinugroho et al. (2015) with a value of P=0.250 and Apsari et al. (2018) with a value of P=1,00.[19]

The use of standard masks recommended by NIOSH for mining workers, there are two basic principles, namely a respirator preventing particles from entering the airway, the second is called air-purifying respirators. for dust particles, the use of respirators is the simplest type, and the simplest recommended is the use of N95 masks.[32] Research conducted by Khumaidah (2009) on 44 furniture workers showed different results in the form of a significant relationship between the use of PPE and pulmonary function disorders. Workers who do not use PPE in the form of masks have a risk of pulmonary disorders of 6 times compared to workers who use PPE masks.[33]

Analysis of the relationship between work location and pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency P=0.065 because the majority of research subjects work in the limestone mine, namely 66 people compared to 7 people in the limestone mill, but after multivariate analysis Work location is the third risk factor for pneumoconiosis because the dust mill is the location with the highest dust content, which is 223.3 mg/m^3 because the limestone mill is a closed room so that dust can not be blown away by the wind. This study is in accordance with the research of Simanjuntak et al. (2015) conducted research on cement collecting workers in the cement packing unit of PT. The Tonasa Line of Bitung City at that location using dust measurements with a personal dust sampler obtained 28 subjects (73.6%) of 38 subjects exposed to high dust levels >3 mg/m^3.[20]

The results of the analysis of lung function variables on the incidence of pneumoconiosis in this study did not show relationship between lung function and pneumoconiosis with a value of P=0.235 in VC, P=0.705 in %VC, P=0.238 for FVC, P=0.683 at %FVC, P=0.170 for FEV_1, P=0.649 for %FEV_1 and P=0.141 for %FEV_1/FVC. Compared to the research of Damayanti et al. On cement workers PT. X, it was found that 56 workers (30.8%) had pulmonary function abnormalities in the form of restriction disorders 35 people (19.2%) 15 people (8.2%) obstruction disorders (8.2%) and mixed disorders 6 People (3.3%).[9]

Research conducted by Zhu et al (2017) on 75 workers with silicosis from the same molybdenum mine in a small Chinese town proved that silicosis was radiographically significant in all parameters between stages I, II, and III. Zhu et al. (2017) also found that increasing the extent of silicotic lesions associated with regions had a more significant reduction in pulmonary function with progressive massive fibrosis in FEV_1, FEF_{75}, FEF_{50}, and FEF_{25} (P<0.05).[34]

Research conducted by Tonori et al. (2005) also showed similar results, namely KV and FEV_1 in workers with lower silica exposure compared to workers who were not exposed to silica and asbestos (P<0.001).[35] The results of Ergun et al. (2017) also showed that There was a significant association between pulmonary function disorders and all radiological abnormalities, namely chest X-ray and High Resolution Computed Tomography (HRCT) for dental technicians with nodular perfusion (NP) values for chest X-ray

are FVC (r=-0.448; P<0.001) and FEV_1 (P<0.001; r=-0.460). NP values for total score are FVC (r= -0.499; P<0.001): FEV_1 (r=–0.446; P<0.001). And NP values for opacity score parenchyma are FVC (r=-0.417; P<0.001), FEV_1 (r=-0.400; P<0.001).[36]

Research conducted by Nij et al (2013) conducted on 64 mining workers in the UK also showed similar results to this study, namely that there was no significant relationship between pulmonary function and radiological features in patients with pneumoconiosis (P=0.09). This differences can be caused by the small opacity class and density of silicosis there is no significant difference in pulmonary function parameters.[34,37]

CONCLUSION

The proportion of pneumoconiosis in limestone mining workers in Citatah Village, West Bandung Regency is 15.1%. Characteristics of limestone mining workers in Citatah, West Bandung Regency, median age of 42 years, the majority of workers are male, the majority of workers are in primary school, the majority of workers work ≥8 hours, the majority of workers are smokers, the majority of workers' nutritional status is normal, the majority of workers have worked <6 years , the majority of workers do not use masks, the majority of workers' pulmonary functions are normal, the highest level of company dust is 223.30 mg/m^3 and the majority of workers work in a limestone mine. The factors that influence the incidence of pneumoconiosis are length of work and dust level.

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ORIGINAL ARTICLE

The Effect Of Soluble CD14 Subtype (sCD14ST)/Presepsin And Lactate Clearance On Mortality Status In Pneumonia Patients With Sepsis

Zikanovelia[1], Ngakan Putu Parsama Putra[1], Yani Jane Sugiri[1], Harun Al Rasyid[2]

[1]Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Brawijaya/ RSUD Dr. Saiful Anwar, Malang
[2]Department of Department of Public Health Sciences and Preventive Medicine, Faculty of Medicine, Universitas Brawijaya/RSUD Dr. Saiful Anwar, Malang

ABSTRACT

Background: Severe pneumonia accompanied with sepsis could increase death ratio by 7.6%. Lactate clearance is used in assessing the success of early resuscitation in treating sepsis. Presepsin is a biomarker that is sensitive and specific to the bacterial infection that causes sepsis. The purpose of this study was to analyze the effect of presepsin levels and lactate clearance on mortality in pneumonic patients accompanied with sepsis after fourteen day of observation.

Method: Prospective cohort study was done on 42 community acquired pneumonia patients who were admitted to intensive care unit of dr. Saiful Anwar Public Hospital, from March 2019 until May 2019, and were treated following the PDPI guideline. Blood samples were collected on the first, second, and third day of treatment to measure lactate clearance and presepsin levels. Mortality was observed on the 14th day after admittance.

Results: Out of 42 patients, 25 patients lived (59.5%), and 17 patients died (40.5%). Logistic regression analysis performed on the presepsin levels on the third day with a cut-off 957 ng/L had a significant effect on mortality after 14th day (P=0.034). However, presepsin levels on the first day with a cut-off 957 ng/L had no significant effect on mortality (P=0.24). Likewise, the lactate clearance with cut-off 10% did not significantly influence the mortality status (P=0.136).

Conclusion: There is a significant effect between presepsin level on the third day in patient mortality, however lactate clearance and presepsin level assessed on the first day had no significant effect on the mortality after fourteen day of observation.

Keywords: pneumonia, sepsis, presepsin, lactate clearance, mortality

*Correspondence: Zikanovelia - zikanovelia@gmail.com

Submitted: February 4th 2021, Accepted: February 22th 2021, Published: February 28th 2021

INTRODUCTION

Lower respiratory infection is the main cause of death worldwide; one of the lower respiratory tract infections that often occurs is pneumonia. In Indonesia, the prevalence of pneumonia in 2013 reached 4.5%.[1] Pneumonia is one of the top 10 causes of hospitalization with a higher Crude Fatality Rate (CFR) of 5.2%.[2]

Sepsis is a serious health problem and is one of the top ten causes of death in the world. Still, the initial diagnosis of sepsis is often difficult to establish because the clinical presentation of sepsis is very diverse.[3] Clinical assessment of sepsis can use qSOFA (quick sequential (sepsis-related) criteria.[4]

Organ Failure Assessment) score to assess the degree of severity of sepsis based on the involvement of the organ failure that occurred. The importance of early detection of sepsis, not only with the clinical parameters where patients often present with severe conditions, but also biochemically as a diagnostic tool and monitoring therapy.[4]

Presepsin or sCD14-ST, has recently been proposed as a biomarker of sepsis. Presepsin was first recognized in 2005 and has become a new important biomarker for the diagnosis and prognosis of sepsis in recent years.[5]

Also, the most widely studied biomarker and the basis for the development of sepsis treatment is lactate levels. In patients with severe sepsis, lactate has a good role in the aspects of diagnosis, initiation of resuscitation, final parameters of resuscitation, and even in determining prognosis.[6]

Researchers are interested in examining presepsin and serum lactate among other sepsis biomarkers because presepsin is a promising new biomarker, is cost-effective and can diagnose precisely and accurately prognostic sepsis, as well as a superior prognostic marker than procalcitonin. Therefore, the investigators are interested in examining the levels of presepsin biomarkers, serum lactate in pneumonia patients with sepsis.

Previous studies about sepsis studies have examined presepsin and lactic acid, but not specific to pneumonia, using Elisa as the average method, however this study specifically foused on pneumonia, and chemiluminescent enzyme immuno-assay (CLEIA) was used instead of ELISA to measure presepin levels. This study took 14 days of research, whereas other studies took an average of 30 days.

METHOD

This study was conducted using a prospective cohort observational method to determine the relationship between presepsin and lactic acid with the mortality status of pneumonia patients with sepsis who were hospitalized in the intensive care unit. The study was conducted from December 2019 to May 2020 in the Emergency Room and Respiratory High Care Unit/Intensive Care Unit at Dr. Saiful Anwar Malang.

The sample population was community acquired pneumonia patients with sepsis who were hospitalized in the Respiratory High Care Unit/Intensive Care Unit at Dr. Saiful Anwar Malang. According to the formula, the minimum sample size is 40 people.[7] The Ethical Commitee Medical Reseacrh of Brawijaya University had granted ethical approval for this study.

Patients with community acquired pneumonia are diagnosed from anamnesis, physical examination, CXR, and laboratory examination. Diagnosis are obtained in which the patients shows one of following cases: infiltrate or air brochogram found in CXR and several symptoms, such as cough characteristic change in sputum/purulent sputum, axillar temperature of ≥38^{o}C or history of fever, chest pain, shortness of breath, physical examination showing signs of consolidation, bronchial breath sound, and rhonki, and leucocyte of ≥10,000 or <4,500.[1]

Criterias of sepsis applied to subjects are following the sepsis guideline. In 2016, the Sepsis-3 Task Force updated previous recommendations primarily aiming to accurately differentiate between sepsis and uncomplicated infection. By applying a data-driven approach to identify patients at risk of worse outcomes, the Task Force proposed a new clinical definition, removing the need for systemic inflammatory response syndrome (SIRS) criteria. Thus, in infected patients, sepsis was clinically defined by an increase in Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of two points or more. Additionally, a bedside score for risk stratification, namely the quick SOFA (qSOFA), has been proposed, which incorporates hypotension, altered mental status, and tachypnea.[4]

Samples were obtained using consecutive sampling in pneumonia patients with sepsis who were hospitalized in the intensive room at Dr. Saiful Anwar Malang who met the inclusion and exclusion criteria. The inclusion criteria in this study were pneumonia patients with sepsis who

were hospitalized in the intensive room at Dr. Saiful Anwar Malang who is ≥18 years old and the patient and/or his family are willing to take part in the research and sign an "informed consent". Patients with HIV-AIDS, pregnancy, CKD st III, chronic liver disease, and pneumonia patients with sepsis who died before the third day of hospitalization were not included in this study.

Forty-two patients who met the inclusion and exclusion criteria and signed informed consent were measured the levels of lactate clearance on the first and second day of hospitalization, presepsin levels on the first and third day of hospitalization, and observed patient mortality on the fourteenth-day hospital treatment. Patients were treated following the PDPI guideline, wherein patient's treatments were adjusted to patient's conditions. The subjects were either given antibiotics to drink at home, hospitalized, or subjected to intensive care unit.[1]

Processing and data analysis using IBM SPSS version 24.0 software. To see the relationship between lactate clearance, perceptions of H1 and H3 with patient status, the Chi-square correlation test was used. To see the effect of lactate clearance, perception of H1 and H3 on mortality in pneumonia patients with sepsis, a logistic regression test was used.

RESULT

Based on the recapitulation of the basic data of research subjects, it was found that the research subjects were more male; namely 23 people (55%) than 19 women (45%), aged between 23 to 91 years with the largest age distribution between 57 and 73 years, that is 19 patients or 45%.

Of the 42 study subjects, there were 39 study subjects (93%) who had comorbid diseases, whereas comorbid diseases did not accompany only 3 patients (7%). Of the 39 patients who had comorbid, 22 patients survived, and 17 patients died. A total of 3 patients without comorbid disease survived the 14-day evaluation. From Figure 1, it can be seen that there are various comorbid diseases.

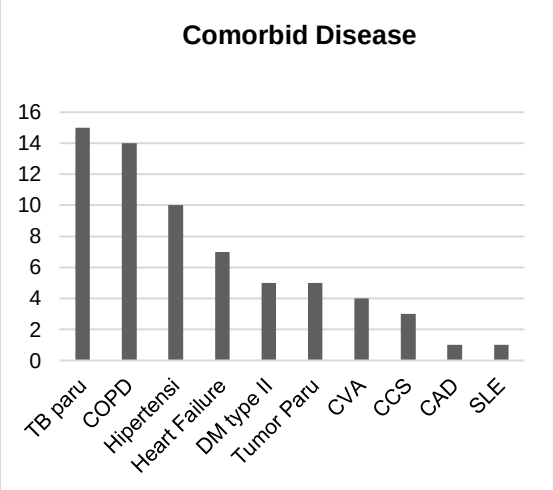

Figure 1. Characteristics Based on Cormobid Diseases

Table 1. Characteristics of Research Subjects

Characteristics	Alive (n=25)	Died (n=17)	Total (n=42)
Gender			
Male	16 (38%)	7 (17%)	23 (55%)
Female	9 (21%)	10 (24%)	19 (45%)
Age (years)			
23-39	2 (5%)	1 (2%)	3 (7%)
40-56	6 (14%)	6 (14%)	12 (29%)
57-73	11 (26%)	8 (19%)	19 (45%)
74-91	6 (14%)	2 (5%)	8 (19%)
Marital Status			
Married	25 (60%)	17 (40%)	42 (100%)
Single	0 (0%)	0 (0%)	0 (0%)
Smoker			
Yes	9 (22%)	11 (26%)	20 (48%)
No	16 (38%)	6 (14%)	22 (52%)
Education			
No School	1 (2%)	0 (0%)	1 (2%)
Elementary School	9 (21%)	8 (19%)	17 (40%)
Junior High School	6 (14%)	4 (10%)	10 (24%)
Senior High School	7 (17%)	4 (10%)	11 (27%)
Bachelor	2 (5%)	1 (2%)	3 (7%)
Profession			
College Student	1 (2%)	0 (0%)	1 (2%)
Laborer	1 (2%)	0 (0%)	1 (2%)
Swasta/Private	12 (28%)	11 (26%)	23 (55%)
Farmer	1 (2%)	2 (5%)	3 (7%)
Housewife	5 (12%)	4 (10%)	9 (21%)
Retired	3 (7%)	2 (5%)	5 (12%)
Comorbid			
No	3 (7%)	0 (0%)	3 (7%)
Yes	22 (52%)	17 (41%)	39 (93%)
Sputum Culture			
Germs (+)	14 (33%)	12 (29%)	26 (62%)
Germs (-)	0 (0%)	0 (0%)	0 (0%)
Sample (-)	11 (26%)	5 (12%)	16 (38%)
Blood Culture			
Germs (+)	4 (10%)	8 (19%)	12 (29%)
Germs (-)	21 (50%)	9 (21%)	30 (71%)
Sample (-)	0 (0%)	0 (0%)0	0 (0%)

Table 3. Chi-Square Analysis

Variable	Cut Off	Patient Status				OR (95%CI)	P
		Alive (n=25)		Dead (n=17)			
Lactate Clearance	<10%	10	24%	13	31%	4,87	0,02
	≥10%	15	36%	4	9%	(0,51-0,84)	
Presepsin H1	<957	15	36%	5	12%	3.60	0,051
	≥957	10	24%	12	28%	(0,48-0,82)	
Presepsin H3	<957	16	38%	3	7%	8,29	0,003
	≥957	9	22%	14	33%	(0,57-0,88)	

After measuring the marker values for lactate clearance and presepsin on the first and third day, the patients were assessed for their mortality status on the fourteenth day. Descriptive analysis of the lactate clearance and preseptin values was carried out; then the data were presented in the form of cross-tabulations as follows Table 2.

Table 2. Descriptive Analysis

Biomarker	Alive (n=25)	Dead (n=17)	Total (n=42)
Presepsin H1			
<957	15 (36%)	5 (12%)	20 (48%)
≥957	10 (24%)	12 (28%)	22 (52%)
Presepsin H3			
<957	16 (38%)	3 (7%)	19 (45%)
≥957	9 (21%)	14 (34%)	23 (55%)
Lactate Clearance			
<10	10 (24%)	13 (31%)	23 (55%)
≥10	15 (36%)	4 (9%)	19 (45%)

Chi-square analysis was used to see the relationship between lactate clearance, Presepsin day one and day three of the patient's mortality status. From the results of the chi-square analysis in Table 3.

The results of the analysis of the Lactate clearance examination with the patient's mortality status were seen with the chi-square analysis, and the P=0.020. So, it can be concluded that there is a significant relationship between lactate clearance and patient mortality status.

Based on Table 3, it is found that the odds ratio is 4,875, which means that a lactate clearance> 10% tends to become a live patient, 4,875 times greater than that of a dead patient. Or it can be said that a lactate clearance of ≥10% tends to be a patient in the live category, and lactate clearance of <10% has a tendency to the status of a patient in the dead category.

Analysis of the results of the examination of Presepsin H1 with the patient's mortality status seen by chi-square analysis obtained P=0.051, the H0 decision was accepted. So it can be concluded that there is an insignificant

relationship between Presepsin H1 and patient status.

Based on Table 3, it is found that the odds ratio is 3,600, which means that Presepsin H1 <957 ng/L tends to live category patients 3,600 times greater than that of dead patients. Or it can be said that Presepsin H1 <957 ng/L tends to the patient status in the life category, and Presepsin H1 ≥957 ng/L has a tendency to the status of the patient in the dead category.

Analysis of the results of the examination of Presepsin H3 with the patient's mortality status seen by chi-square analysis obtained the P=0.003, the H0 decision is rejected. So it can be concluded that there is a significant relationship between Presepsin H3 and patient status.

Based on Table 3, it is found that the odds ratio is 8,296, which means that Presepsin H3 <957 ng/L tends to live category patients 8,296 times greater than the status of patients with a dead category. Or it can be said that Presepsin H3 <957 ng/L tends to the patient status in the life category, and Presepsin H3 ≥957 ng/L has a tendency to the status of the patient in the dead category.

Logistic regression analysis was used to see the effect of lactate clearance, Presepsin on the first and third day of the patient's mortality status. From the logistic regression results in Table 4.

The Lactate clearance variable has 2 categories, namely ≥10% and <10%. Based on the analysis, it was found the P=0.136 indicating that there was no significant effect of the Lactate clearance variable on the patient's mortality status.

The coefficient obtained for category 1 (<10%) is positive (B=1.159), and from the beta exponential value of 3.187, it shows that if the Lactate clearance variable is <10%, the tendency for the patient status variable in the category of death is 3,187 times greater than the patient status variable in the life category. Uncertain because the effect showed insignificantly.

Table 4. Logistic Regression Analysis Result

Variable	B	Wald	P	OR	Information
Lactate clearance	1.159	2.222	0.136	3.187	Not Significant
Presepsin H1	0.880	1.337	0.248	2.410	Not Significant
Presepsin H3	1.707	4.501	0.034	5.510	Significant

Presepsin H1 variable has 2 categories, namely <957 and ≥957. Based on the analysis, it was found P=0.248 indicating that there was no significant effect of the Presepsin H1 variable on the patient status variable. The coefficient obtained for the category of death (≥957) is positive (B=0.880), and from the beta exponential value of 2.410, it shows that the Presepsin H1 category is ≥957, the tendency for the patient status variable in the category of death is 2,410 times greater than the variable for the patient's status in the uncertain life category because the effect shows insignificant.

Presepsin H3 variable has 2 categories, namely <957 and ≥957. Based on the analysis, it was found P=0.034 indicating that there was a significant effect of the Presepsin H3 variable on the patient status variable. The coefficient obtained by the category of death (≥957) is positive (B=1.707), and the beta exponential value of 5,510 shows that if the Presepsin H3 variable category ≥95, the tendency for the patient status variable in the category of death is greater 5,510 times compared to the patient status variable in the life category. Ascertained because the effect showed a significant effect.

DISCUSSION

This study showed that pneumonia patients studied more male gender compared to women. But the percentage of comparison is only slightly different than of male sufferers compared to women (55% versus 45%). This is in accordance with observational research by Nasir et al. in 2015, showing that the prevalence of pneumonia in Pakistan is more prevalent in men than in women (54% compared to 46%).[7] The same thing was also shown in a retrospective study of germ patterns at Dr. Saiful Anwar Hospital Malang in 2018, male pneumonia sufferers more than women (58.43% compared to 41.6%).[8]

Men are more likely to suffer from pneumonia than women because it is suspected that men are more often out of the house so that it is more easily contaminated/infected with germs or viruses, and the number of pathogenic substances in the form of cigarettes and others that are consumed more by men. This can lower the body's immune system, making it more susceptible to pneumonia, compared to women who are mostly housewives and usually only at home so rarely exposed to polluted air.[9]

The incidence of pneumonia increases with age, and more than 90% of deaths from severe pneumonia

occurring in patients over the age of 70. In Ramirez et al.'s study in the United States from 2014 to 2016, the prevalence of pneumonia was most prevalent among the ≥ 65-year-old age group of 2000 per 100,000 inhabitants in the United States.[10]

In this study, the 57-73-year-old age group had the highest prevalence of pneumonia with sepsis. This is also in accordance with research conducted by Azmi et al. in Malaysia, Indonesia, and the Philippines, which shows that the 66-80-year-old age group has the highest prevalence in Indonesia of pneumonia with sepsis.[2]

The prevalence of severe pneumonia accompanied by sepsis, mostly in the age range of elderly >65 years, is caused by various factors including the body's weakened immune system with increasing age, has many comorbid factors including chronic obstruction pulmonary disease (COPD), lung cancer, diabetes mellitus, cerebrovascular diseases, heart failure, and others. The manifestations of clinical symptoms experienced are also not typical and cause falls into critical condition and require intensive care in hospital.[11]

The subject of this study also obtained many comorbid diseases/participants. From the 42 patients showed 39 patients had comorbid, and each had more than one comorbid. Only 3 patients have no comorbid at all. From the research data of 3 patients were able to survive until the 14th day of observation. This suggests comorbid factors will aggravate pneumonia with sepsis and tend to increase mortality. The containment of comorbid disease itself can also increase production and decrease lactate cleansing in the body.[12,13]

In this study, three of the most common comorbidities were pulmonary TB, COPD, and heart failure. In patients with pulmonary TB, lactate is also produced in response to infections that are the result of anaerobic glycolysis and help kill *Mycobacterium tuberculosis* intracellularly. COPD also increases lactate levels related to increased respiratory muscles that occur during an acute exacerbation. Lactate is also associated with the inadequate perfusion of tissue that occurs in heart failure.[12,13]

The etiology of pneumonia from the results of sputum culture in this study was most caused by *Klebsiella pneumonia* as many in as 7 patients, and some others were also caused by gram-negative basil. This is also reinforced from data from several hospitals in Indonesia in 2012 showed that the most common causes of

community pneumonia in the inpatient room of the sputum material were gram-negative germs such as *Klebsiella Pneumonia*, *Acinetobacter baumanii*, *Pseudomonas aeuruginosa* while gram positives such as *Streptococcus pneumonia*, *Streptococcus viridans* were found in small quantities. From germ pattern research data in RSSA in 2018, the results of sputum showed Germ *Klebsiella pneumonia* was found in 220 sputum samples.[1,8]

The results of germ type data in this study and from the data of various hospitals are slightly different from Infection Diseases of America/American Thoracic Society (IDSA/ATS) data that illustrates that the percentage of germs that cause community pneumonia is greater by gram-positive than gram-negative. This may be due to the research subjects at Dr. Saiful Anwar Hospital Malang, most of them referral patients who have been hospitalized for several days in primary hospitals with severe conditions and referred to RSSA. Possible germs cause can come from germs contained in the treatment place/ICU hospital before or from the Hospital Dr. Saiful Anwar Malang itself.

The percentage of positive blood culture in this study was 28.5%. The same results were also obtained in research conducted by Yana et al. at Hasan Sadikin Hospital in 2017 obtained a percentage of positive blood culture in sepsis patients of 24%. The figure is still low, and this is because the time of blood collection for culture is still >6 hours, and most research subjects have been given antibiotics before taking blood culture.

Lactate clarance examinations are categorized as <10% and ≥10%. The results of this study showed that lactate clearance with patient mortality status had an insignificant influence. It can be seen from the analysis of logistic regression statistical value is P=0.136.

Research on lactate clearance has been widely done. Some studies have shown that lactate clearance is a significant factor in predicting the death of patients with sepsis. Surviving Sepsis Campaign 1 hour-bundle establishes the first step of resuscitation management in sepsis and sepsis shock patients is to measure lactic levels, in case of an increase in early lactate levels of ≥4 mmol/L is required fluid resuscitation treatment, and it is recommended to measure lactate levels again to assess the therapeutic response.[14]

Although many studies have used lactate clearance as a good marker in estimating a patient's mortality status, Hernandez et al. said there are still doubts and vagueness in their clinical use, related to the definition of

clearance/cleansing itself is the expenditure of substance/product from blood measured by volume per time (ml/minute). Changes in lactate levels occur due to the production and cleansing of the blood through excretion and lactic metabolism.[15] According to a review of research by Vincent et al. measuring lactic levels of 1-2 hours will provide accurate and clinically accurate data on lactate levels reduction compared to measuring lactate clearance.

The >10% lactate clearance cut-off was first proposed by Nguyen et al. based on his research that lactate clearance >10% has the ability to predict deaths within 60 days of sepsis patients. Other research was also conducted by Hambali et al. on-sepsis patients treated in RSCM intensive care. This study obtained a higher survival rate in the group of patients with high lactate cleansing compared to the low lactate cleansing group. In other words, patients with low lactate cleansing had a higher risk of death than patients with high lactate cleansing. Based on the analysis of survival rate in the group of patients with high lactate clearance was 60.0% and in the group of patients with low lactate clearance of 26.7%.[16,17]

Research conducted by Choudary et al. showed lactate clearance <10% in the first 24 hours has a sensitivity and specificity of 78.7% and 72.2%, and it has a positive predictive value of 83.1%. Inability to achieve lactate clearance levels ≥ 10% is associated with a high risk of death (likelihood ratio=2.83;=, 95% CI=1.82-4.41).[18]

A meta-analysis conducted by Zhang et al. by analyzing various studies in 2014 illustrates that optimal lactate clearance can provide a low mortality rate in sepsis (critically ill) patients in the ICU. Overall sensitivity and specificity values of lactate clearance in predicting death 0.75 (95% CI=0.58-0.87) and 0.72 (95% CI=0.61-0.80). The prognostic lactate clearance ability devoted to sepsis patients in ICU was seen to increase in the meta-analysis research conducted by Zhang et al. namely with sensitivity and specificity of 0.83 (95% CI=0.67-0.92) and 0.67 (95% CI=0.59-0.75). This prognostic lactate clearance capability is very meaningful for clinical benefit.[19]

Various studies on lactate clearance of patients with sepsis in ICU showed significant results in prognostic ability/survival rate in patients with sepsis treated in ICU. The study conducted by Nguyen et al. evaluated lactate clearance levels on the first day and 72 hours later, then assessed the patient's death at 28 days. In this study, slightly different observation/

assessment of patient death is not done on day 28, but rather on the 14th day in the acute phase.

Research meta-analysis by Zhang et al., showed many studies are still not homogeneous in determining the cut-off of marker lactate clearance, the study subjects in some studies were also not specific to assess patients with the source of infection in the lungs. Various confounding factors in some studies can also have the potential to obscure the results of the research.

In this study, the study subjects taken were patients who were treated in intensive care and mostly had comorbid disease factors. In one patient, there can be more than one comorbid. The containment of comorbid disease itself can also increase production and decrease lactate cleansing in the body.[12,13]

However, clinical use of lactate clearance is still used today in patients with sepsis and sepsis shock. The increase in lactate levels is a sign of how the clinical outcomes of patients and the rapid and good lactate clearance are widely associated with increased outcome/ survival rate in patients in ICU with critically ill.

H1 Presepsin examination is categorized <957 and ≥957. The results of this chi-square test showed an insignificant relationship between presepsin H1 and patient mortality status (P=0.020, OR=3,600, 95% CI=(0.483-0.823). According to the logistic regression test, there was no influence between presepsin and patient mortality with a statistical score less than the chi-square value (1,337<3,841).

H3 Presepsin examination is categorized into <957 and ≥957. The results of this chi-square test showed a significant relationship between H3 Presepsin and patient mortality status (P=0.003, OR=8,296, 95% CI=0.576-0.888). According to the logistic regression test, the influence between presepsin and mortality of patients with statistical value is greater than the value of chi square (4,501>3,841). Research conducted by Yu et al. in 2017 that evaluated the therapeutic effectiveness and prognosis of presepsin and procalcitonin dynamically within 12 days. The results showed that presepsin has a better relationship with SOFA score compared to procalcitonin. A decrease in high presepsin rates has a significant relationship with survival rates in patients with sepsis.[20]

Presepsin is a biomarker specific to bacterial infections due to the onset of monocyte/macrophage-specific CD14 receptor complex bonds after LPS bonding with CD14. Presepsin also increased in patients with positive

cultures on microbiological examinations and in inappropriate antibiotic therapy. Therefore, dynamic presepsin monitoring helps to evaluate infections.[21]

Research showing significant presepsin prognostic value in patients with sepsis with sensitivity figures: 71-72%, specificity: 70-86%, and NPV: 52-71%.[20] For cut-off determination there are still many who are not suitable, for example in El Said et al. research, the best prognostic cut-off is at 2100 pg/ml with a sensitivity of 92%, specificity of 83% and accuracy of 88%. In this study took a cut-off conducted by Ali et al. where presepsin ≥957 has sensitivity and specificity of 94.7% and 85.7% and has a predictive positive value of 90% in predicting the death of patients with sepsis.[22]

Other studies that show the same thing that in presepsin show a significant relationship with patient mortality. Carpio et al. said that presepsin in the living group had a median value below 600 ng/L and decreased significantly from the initial score at the 72-hour evaluation. However, in the deceased group, the median score showed high results >1700 ng/L, and it showed an increase in value at the evaluation 72 hours later. Behnes et al. report that presepsin is useful for viewing the patient's prognosis on the first and third days of treatment. In living patients, presepsin levels were higher on the first day compared to the third day of treatment. Similarly, Carpio et al. said median presepsin levels in patients who survived were higher on the first day than after 72 hours after the day of treatment.[23]

In this study, the presepsin levels of the first day of treatment showed that there was an insignificant relationship and had no effect on the mortality status of the patient. This can be caused by the research subject factor, which is mostly a referral patient from the previous primary hospital to Dr. Saiful Anwar Malang Hospital, which is a tertiary hospital. The patients usually get pneumonia therapy and treatment by the hospital before, so it can affect the value of presepsin on the first day of treatment at RSSA. This may also be related to the relationship of presepsin levels with patient mortality status.

On the third day of treatment pneumonia patients with sepsis who are treated in the RSSA, the intensive room has received therapy according to the guidelines for the management of pneumonia patients with sepsis who are treated in intensive care and performed treatment if there is a comorbid factor. Empirical antibiotic administration

patterns look at germ patterns in the RSSA intensive room and also make definitive antibiotic adjustments if there have been patient culture results and in accordance with germ resistance to antibiotics. Presepsin levels measured on the third day showed a significant link to the patient's status, and this third-day preceptual rate had an influence on the mortality status of the patients studied.

CONCLUSION

First-day presepsin levels in pneumonia patients with sepsis have an effect on the mortality status of pneumonia patients with sepsis within 14 days, but this influence is not statistically significant. Third day prespsin levels in pneumonia patients with sepsis have a statistically significant relationship and influence, so it can be used to predict patient the mortality within 14 days in cases of pneumonia with sepsis. Lactate clearance in pneumonia patients with sepsis has a link and influence on mortality status of pneumonia patients with sepsis within 14 days, but this influence is not statistically significant.

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ORIGINAL ARTICLE

Osteoporosis Proportion In Stable Patients With Chronic Obstructive Pulmonary Disease

Dwi Handoko[1], Faisal Yunus[1], Budhi Antariksa[1], Rochsismandoko[2]

[1]Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta
[2]Department Internal Medicine, Persahabatan Hospital, Jakarta

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in the world. Comorbid diseases in COPD contributing to low health status, affecting the duration of treatment and even death. Osteoporosis is a quite often comorbid that found in COPD. In Indonesia, there are no data of prevalence on osteoporosis in patient with stable COPD. The aim this research to get the data of osteoporosis in patients with stable COPD at Persahabatan Hospital.

Method: The studie's design was cross-sectional. Patients with stable COPD who came to the Asthma/COPD policlinic at Persahabatan Hospital who meet the criteria of inclusion and exclusion. Subjects had an examined of bone mineral density using dual energy x-ray absorptiometry (DXA) and had an examined of vitamin D blood level. At the time of visit, conducted anamnesis of symptoms, exacerbations, history of smoking, used of corticosteroid (oral or inhaled), comorbid, assessment of nutritional status.

Results: Subjects were dominated with male (90.6%) in the age group 65-75 years old (53.1%), and smoking history (84.4%). The most degree of COPD were GOLD II (46.9%) and group B (50%) that using corticosteroid (65.7%). Prevalence of osteoporosis was 37.5%. There were no statistically significant between COPD group, the degree of COPD, sex, smoking history, history of corticosteroid, age, levels of 25-OHD, pulmonary function with the occurrence of osteoporosis in patients with stable COPD. There were a statistically significant on low BMI as a risk factor for osteoporosis in stable COPD.

Conclusion: The prevalence of osteoporosis in patients with stable COPD in the Persahabatan Hospital is 37.5%. There are a statistically significant relationship between BMI with osteoporosis in patients with stable COPD.

Keywords: COPD, osteoporosis, prevalence, stable

*Correspondence: Budhi Antariksa - antariksab@gmail.com

Submitted: February 14th 2021, Accepted: February 27th 2021, Published: February 28th 2021

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of illness and death in the world. The *global burden of disease study* estimates that COPD is ranked third in 2020 and fourth in 2030 as the cause of death in the world. In the case of COPD, pain is estimated to increase from fourth to third. The prevalence of COPD in the general adult population is estimated at 1%, with a significant increase at age ≥40 years and the prevalence continues to increase alongside with age.[1] Data from the RSUP Persahabatan shows COPD is the fifth rank of outpatient cases and fourth of inpatient cases from 1995-1999.[2]

Chronic obstructive pulmonary disease may cause a variated severity of emphysema, but it is also may cause other systemic effects and comorbidities. Possible systemic effects from COPD are muscle disorders, cahexia, anemia, autonomic disorders and systemic inflammation. Comorbidities in COPD includes cardiovascular diseases, lung cancer, osteoporosis, diabetes and depression.[3]

Osteoporosis is a systemic bone disease, which has the characteristics of bone density loss resulting in high risk of fracture. Vertebral compression fractures are often found in COPD patients which results in decreased lung function.[4,5] Comorbid disease in COPD contributes to low health status, affecting length of treatment and death. There has been no research in Indonesia regarding the prevalence of osteoporois as a comorbid disease in COPD. This study will discuss the prevalence of osteoporosis in stable COPD patients.

The aim this research is investigate the prevalence of osteoporosis in patients with stable COPD who visited the asthma/COPD clinic of RSUP Persahabatan.

METHOD

The design of this study is a observational with cross-sectional study. The study was conducted at the asthma/COPD clinic of RSUP Persahabatan, starting in June 2015 to achieve the specified amount of subjects.

The affordable population are stable COPD patients with mild to severe stable COPD according to the GOLD 2014 criterias who came to the asthma/COPD clinic of RSUP Persahabatan Jakarta.

Subjects were recruited by consecutive sampling, in which every stable COPD patient who met the study criteria and are willing to participate in the study were included until the required amount is achieved.

After history taking and physical examination, patients were determined their COPD severity from mild to very severe and subsequently selected to look for subjects who meet the criteria for acceptance and rejection. The patient is then asked if they are willing to be the subject of the study by first being given an explanation of the purpose and benefits of the study and the way the examination will be conducted. Patients who are willing to become research subjects were asked to fill out and sign a informed consent.

The acceptance criteria this research are stable COPD patients from mild to very severe, both men and women aged 40-80 years who came to theasthma/COPD clinic of RSUP Persahabatan Jakarta and willing to voluntarily follow the whole program of research by providing written consent and signing a informed consent. Meanwhile, the rejection criteria are patients with COPD exacerbations and stable COPD patients who are unwilling to continue after agreeing to join.

Stable COPD patients who meet the admission criteria and are willing to be the study subjects will go through anamnesis, physical examination, and blood tests for vitamin D through measurements of serum levels of 25-hydroxy vitamin D (25-OHD) in the Clinical Laboratory Pramita, followed by the gold standard test of osteoporosis DMT using DXA at RSCM Kencana.

RESULT

This study was a cross sectional study to identify the prevalence of osteoporosis in stable COPD patients. This study was conducted from June to September 2015 in stable COPD patients who came to the asthma/COPD clinic of RSUP Persahabatan Jakarta. The number of subjects in this study were 32 people. Subjects were tested for DMT using DXA equipment at RSCM Kencana and vitamin D examination measured by serum 25-OHD levels through venous blood collection in Pramita clinical laboratory.

The study successfully recruited 32 subjects, most subjects were males with a total of 29 subject (90.6%) compared to women of 3 subject (9.4%), as shown in Table 1. The youngest age is 54.5 years and the oldest is 79.9 years with an average age of 65.78±6.53 years. The highest subject age of the group is 65-75 years as many as 17 people (53.1%), followed by age <65 years with 14 people (43.8%) and age> 75 years with 1 person (3.1%).

Table 1. General characteristics and Clinical characteristics of subjects

Characteristics	n	%
General Characteristic		
Gender		
Man	29	90.6
Woman	3	9.4
Age		
<65 years	14	43.8
65-75 years	17	53.1
>75 years	1	3.1
Education		
Elementary school	10	31.2
Middle school	3	9.4
High school	14	43.8
College	5	15.6
Work		
Retired	9	28.1
Private	19	59.4
Not working	4	12.5
Smoking history		
Former smoker	27	84.4
Not a smoker	5	15.6
Clinical characteristics		
COPD group		
A	2	6.3
B	16	50.0
C	3	9.3
D	11	34.4
Degree of COPD		
I	3	9.4
II	15	46.9
III	10	31.2
IV	4	12.5
Vitamin D levels (25-OHD)		
Deficiency	10	31.2
Insufficiency	11	34.4
Sufficiency	11	34.4
Brink man index		
Light	2	6.3
Medium	11	34.4
Heavy	14	43.7
Do not smoke	5	15.6
Length of COPD		
0-5 years	23	71.9
≥5 years	9	28.1
History of steroid cortico		
Without corticosteroids	11	34.4
Inhaled corticosteroids	21	65.6

Note: COPD=Chronic obstructive pulmonary disease

Table 1. General characteristics and Clinical characteristics of subjects (cont.)

Characteristics	n	%
Use of LABACS		
Budesonide/formoterol (320 µg/day)	10	31.2
Salmeterol/fluticasone propionate, (500 µg/day)	11	34.4
Status of Osteoporosis		
Osteoporosis	12	37.5
Osteopenia	16	50.0
Normal	4	12.5
BMI		
Less	9	28.2
Normal	10	31.2
Overweight	3	9.4
Obesity	10	31.2

Note: COPD=Chronic obstructive pulmonary disease; LABACS=long-actingbeta-2 agonist dengan kortikosteroid; BMI=body mass index

The most prevalent education level of the subjects were high school graduate with 14 people (43.8%) followed by elementary with 10 people (31.2%), college with 5 people (15.6%) and junior high school with 3 people (9.4%). The most prevalent occupation were private workers with 19 people (59.4%) followed by 9 retirees (28.1%) and unemployed with 4 people (12.5%). A total of 27 subject were former smokers (84.4%), and the 5 remaining subjects were non-smoker (15.6%).

Clinical characteristics appear as in Table 1, the results of the subject lung pulmonary examination obtained mean FEV_1 of 49.49±16.40% prediction. The average FEV_1/FVC was 52.87±11.46% prediction. Most of the subjects were group B with 16 people (50%) followed by group D with 11 people (34.4%), group C with 3 people (9.3%) and group A with 2 people (6.3%). Most of the research subjects have a COPD degree II or higher based on GOLD 2014, with degree II or moderate degree of 15 people (46.9%) followed by degree III or severe with 10 people (31.2%), degree IV or very severe with 4 people (12.5%) and degree I or mild 3 people (9.4%). 25-OHD levels were obtained with a mean of 25.45±8.82 ng/ml, 10 people (31, 2%) with deficiency, 11 people (34.4%) with insufficiency and 11 people (34.4%) with a sufficient level.

The highest number of IB Brinkman index is severe with 14 people (43.7%) followed by moderate with11 people (34.4%) and mild with 2 people (6.3%), the rest are non-smokers with 5 people (15.6%). Most subjects suffered from COPD for 0-5

years as many as 23 people (71.9%) and the remaining had COPD ≥5 years with 9 people (28.1%). Most subjects had a history of using inhaled corticosteroids as many as 21 people (65.6%) and 11 people had no history of steroid usage (34.4%).

Subjects using LABACS budesonide/formoterol 320µg/day were 10 people (31.2%) and salmeterol/fluticasone propionate 500 µg / day as many as 11 people (34.4%). In the study, the prevalence of osteoporosis was 37.5%. DMT status based on the assessment of the lumbosacral and hip areas found 16 subjects with osteopenia (50%), 12 osteoporosis (37.5%) and 4 with normal results (12.5%). BMI calculations based on WHO criteria with Asia modification obtained a mean 21.50±5.01 kg/m^2, with 9 subjects classified as underweight (28.2%), 10 normal (31.2%), 3 overweight (9.4%) and 1 with obesity (31.%).

The correlation of subject characteristics with DMT status appears as in Table 2. Age, FEV_1/FVC, Brinkman index, duration of COPD, and inhaled corticosteroid dose did not differ significantly between osteoporosis, osteopenia and normal DMT groups. Median BMI of osteoporosis group was 16.75 (14.00-25.20) kg/m^2, with osteopenia subjects of 23.20 (17.30-32.70) kg/m^2 and normal subjects of 23.10 (19.30-34,20) kg/m^2 with P=0.029, this value is significant for the osteoporosis group compared to normal DMT. The FEV_1% predicted value in osteoporosis group was 45.78±11.05% prediction, followed by osteopenia with 48.51±18.12% prediction and normal subjects with 64.52±18.13% prediction, with significant values for osteoporosis group compared to normal DMT (P=0.025).

Table 4. Correlation of Subject Characteristics with DMT Status

Characteristics	Osteoporosis	Osteopenia	Normal DMT	P
Age (years)	66.54±6.66	64.50±6.45	68.62±6.90	0.599
BMI (kg/m^2)	16.75 (14.00-25.20)[a]	23,20 (17.30-32.70)	23.10 (19.30-34.20)	0.029[a]
Vitamin D (ng/ml)	25.43±10.43	23.35±7.33[b]	33.92±4.07	0.013[b]
FEV_1 (% prediction)	45.78±11.05[a]	48.51±18.12	64.52±18.13	0.025[a]
FEV_1/FVC (% prediction)	53.16±10.06	50.43±11.79	61.72±12.43	0.184
Brinkman index (stem/year)	596.50±555.72	606.88±337.20	864.00±784.57	0.462
Length of COPD (years)	1 (1-15)	2 (1-7)	2 (1-15)	0.840
Dosage of inhaled corticosteroids (µg/day)	320 (0-500)	320 (0-500)	160 (0-500)	0.559

Note: [a]Osteoporosis compared with normal DMT; [b]Osteopenia compared with normal DMT; BMI=body mass index; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; COPD=Chronic obstructive pulmonary disease

The vitamin D level of osteoporosis group was 25.43±10.43 ng/ml, osteopenia was 23.35±7.33 ng/ml, and normal subjects was 33.92±4.07 ng/ml with a value of P=0.013, this value was significant for the group osteopenia compared with normal DMT. These results are not made as conclusions in the study because the distribution is not evenly distributed in each group, so that to conclude the existing data analysis is divided into osteoporosis and non-osteoporosis groups.

Table 3. Fracture risk according to FRAX

	FRAX	
	Major	**Hip**
Mean	1.09	0.08
Median	1.05	0.10
Standard deviation	0.32	0.06
Minimum	0.60	0.00
Maximum	2.00	0.30

Note: FRAX=The Fracture Risk Assessment Score

In this study, 10-year fracture risk will be obtained based on FRAX as in Table 3. At the major FRAX group, the mean value is 1.09 and the mean hip FRAX is 0.08 so this value indicates that the risk is greater in the major FRAX group. The median value of major FRAX major is 1.05 and the hip FRAX is 0.10. The standard deviation of major FRAX is 0.32 and hip FRAX is 0.06. The minimum value of major FRAX is 0.60 and hip FRAX is 0.00. The maximum major FRAX value is 2.00 and the hip FRAX is 0.30. The risk of fracture in the next 10 years appears to be greater overall in major FRAX.

In a study of a total of 32 subjects, the prevalence of osteoporosis in stable COPD patients was 12 people (37.5%) with distribution in each COPD groups as follows group A is 1 person, group B is 5 people, group C is 1 person and group D is 5 people. In the study the prevalence of osteopenia is 16 people (50%) with distribution in each COPD group as follows group A 1 person, group B 7 people, group C 2 people and group D 6 people. The prevalence of subjects with normal DMT status was 4 people (12.5%), all in group B. The prevalence of osteoporosis appears to be comorbid in stable COPD even in group A, as shown in Table 4.

In this study, osteoporosis in stable COPD patients were distributed in COPD degree II or moderate with 6 people, degree III or severe with 5 people, degree IV or very severe with 1 person and no degree I or mild cases. Osteopenia is distributed in grade I or mild COPD with 2 people, degree II or moderate with 6 people, degree III or severe with 5 people and degree IV or very severe with 3 people. The prevalence of subjects with normal DMT status were distributed in first degree or mild COPD with1 person and degree II or moderate with 3 people.

The prevalence of osteoporosis appears mostly in degrees II-III (moderate to severe), as shown in Table 4.

In the study there was no significant relationship between the COPD group with osteoporosis. Distribution of COPD was divided into 2 groups: mild group (group A+B) and severe group (group C+D). Osteoporosis in the mild group is 6 people (50%) and in the severe group is 6 people (50%). Analysis is done by chi-square test, which obtained P=0.581 which means there is no meaningful correlation, as in Table 5.

In this study there was no significant correlation between the COPD degree group with osteoporosis. Distribution of COPD is divided into 2 groups, namely mild group (degree I+II) and severe group (degree III+IV). Osteoporosis in the mild groups were present in 6 people (50%) and the severe group with 6 people (50%). The analysis is done by chi-square test, which obtained P=0.581 showing no meaningful correlation, as in Table 5.

Table 4. The prevalence of osteoporosis in stable COPD groups and degree of COPD

DMT status		Osteoporosis		Osteopenia		Normal		Total	
		n	%	n	%	n	%	n	%
COPD group	A	1	50.00%	1	50.00%	0	0.00%	2	100.00%
	B	5	31.20%	7	43.80%	4	25.00%	16	100.00%
	C	1	33.30%	2	66.70%	0	0.00%	3	100.00%
	D	5	45.50%	6	54.50%	0	0.00%	11	100.00%
Degree of COPD	I	0	0.00%	2	66.77%	1	33.33%	3	100.00%
	II	6	40.00%	6	40.00%	3	20.00%	15	100.00%
	III	5	50.00%	5	50.00%	0	0.00%	10	100.00%
	IV	1	25.00%	3	75.00%	0	0.00%	4	100.00%
Total		12	37.50%	16	50.00%	4	12.50%	32	100.00%

Note: COPD=Chronic obstructive pulmonary disease

Table 5. Correlation between stable COPD and osteoporosis groups

Group	Osteoporosis		Total	OR (95% CI)	*P* value
	Yes	No			
COPD group					
Mild (A + B)	6	12	18	0.67	0,581 *
Severe (C + D)	6	8	14	(0.16-2.82)	
Degree Group					
Mild (I + II)	6	12	18	0,67	0,581 *
Severe (III + IV)	6	8	14	(0.16-2.82)	

Note: *Chi-square test; COPD=Chronic obstructive pulmonary disease

Table 6. Correlation between risk factors with osteoporosis in stable COPD patients

Risk Factors	Osteoporosis		OR (95% CI)	P
	Yes	No		
Gender				
Man	9	20	0.31 (0.18-0.53)	0.044[a]
Woman	3	0		
Smoking history				
Former Smoker	8	19	0.10 (0.01-1.09)	0,053[a]
Not a smoker	4	1		
Steroid history				
Corticosteroids	9	12	2,00 (0,41-9,70)	0,465[a]
Without corticosteroids	3	8		
Age (year), mean (SD)	66.54 (6.67)	65.32 (6.58)	-	0.618[b]
BMI (kg/m^2), median (min-max)	16.75 (14.0-25.2)	23.20 (17.3-34.2)	-	<0.001[c]
25-OHD level (ng/ml), mean (SD)	25.43 (10.44)	25,47 (7,99)	-	0.991[b]
FEV_1 %prediction, mean (SD)	45.78 (11.06)	51.71 (18.83)	-	0.330[b]
FEV_1/FVC %prediction, mean (SD)	53.17 (10.06)	52,69 (12,48)	-	0.912[b]

Note: [a]Chi square test, [b]unpaired T test, [c]Mann Whitney test

The correlation between risk factors for osteoporosis in patients with stable COPD in this study is shown in Table 6. In the osteoporosis group, 9 were male and 3 were female. In the non-osteoporosis group, all 20 of them were male. After further analysis, we obtained a significant correlation between sex and osteoporosis with a value of P=0.044, but this does not describe the actual population because there were only 3 female subjects.

In the osteoporosis group, 8 were former smokers and 4 were nonsmokers. In the non-osteoporosis group, 19 were former smokers and 1 was a nonsmoker. After analysis, P=0.053 was obtained which means there was no significant correlation between smoking history and osteoporosis. In the osteoporosis group, 3 had a history of corticosteroid usage and 9 had no history of steroid usage.

In the non-osteoporosis group, 8 had a history of corticosteroid usage and 12 had no history of steroid usage. After analysis, P=0.465 was obtained showing no significant correlation between corticosteroid history and osteoporosis. The mean age of subjects in the osteoporosis group was 66.54±6.67 years while in the non-osteoporosis group it was 65.32±6.58 years. After analysis, P=0.618 was obtained showing no significant correlation between age and osteoporosis. In the study, we obtained a median BMI of 16.75 (14.0-25.2) kg/m^2 in the osteoporosis group and 23.20 (17.3-34.2) kg/m^2 in the non-osteoporosis group. Analysis showed

P<0.001, revealing a significant correlation between BMI and osteoporosis.

In this study, the mean level of 25-OHD for the osteoporosis group was 25.43±10.44 ng/ml and 25.47±7.99 ng/ml in the non-osteoporosis group. Analysis showed P=0.991, revealing no significant correlation between 25-OHD levels and osteoporosis. Value of FEV_1 in osteoporosis group was 45.78±11.06% prediction, while in the non-osteoporosis group it was 51.71±18.83% prediction. Further analysis resulted is P=0.330 showing no significant correlation between FEV_1 and osteoporosis. Value of FEV_1/FVC was 53.17±10.06% in the osteoporosis group and 52.69±12.48% prediction in the non-osteoporosis group. After analysis, P=0.912 was obtained showing no significant correlation between FEV_1/FVC and osteoporosis.

DISCUSSION

In this study the number of subjects who met the inclusion criteria and participated in this study were 32 people. The basis for calculating subjects in this study was determined based on quantitative data, namely the range of prevalence of osteoporosis in stable COPD patients around 9-69%.[6] Table 3 describes the correlation of osteoporosis, osteopenia and normal DMT, but for the statistical analysis used as the conclusion of this study, we divided them into osteoporosis and non-osteoporosis groups as in the following tables. Our study found an osteoporosis prevalence of 37.5% and 50% if osteopenia. This study supports the finding that the prevalence of osteoporosis in COPD is quite high. We found a significant association between BMI and osteoporosis in stable COPD patients. Osteoporosis is a systemic effect in COPD, but the mechanism is still unclear.

This study found a prevalence of osteoporosis in stable COPD of 37.5% which was obtained using the DXA assessment in 2 locations, namely lumbosacral and hip. This result is similar to the study by Karadag et al. who found a prevalence of 35% in outpatient COPD male patients. Our results are in contrast with Sabit et al, who studied 75 subjects of GOLD I-IV COPD using DXA lumbosacral and hip and found a prevalence of 24%.[7] Graat-Verboom et al who studied 554 subjects of COPD GOLD I-IV using DXA whole-body received a prevalence of 21%.[6] Ferguson et al. who studied 658 subjects of GOLD II-IV COPD using DXA lumbosacral and hip received a prevalence of 24%.[8]

Forli et al on 40 COPD subjects who will undergo lung transplantation

performed DXA lumbosacral and femoral neck and found a prevalence of 59%.[9] A large-scale study by Sin et al on 5215 subjects of COPD GOLD I-IV using DXA total femur found a prevalence of 4-33%. The prevalence of osteoporosis depends on the research method used, the study population and the severity of the underlying respiratory disease. The prevalence of osteoporosis in COPD varies between 9-69%. Overall, the prevalence of osteoporosis is around 35.1% in COPD patients compared to healthy control subjects.[6,10] The relative risk of osteoporosis in COPD patients compared to non-COPD is 3.14.[11]

The prevalence that we get is quite high, which can be explained because there are 3 female subjects whom all had osteoporosis while the remaining 9 people are male, which affects the prevalence obtained. If additional analysis is carried out by removing female subjects, the prevalence obtained is still quite high at 31% compared to the prevalence of the general population of women aged 50-80 years in Indonesia by 23%. Other factors that may influence our study group are the mostly elderly age, low BMI, insufficient levels of 25-OHD and moderate-to-severe pulmonary conditions. Low calcium may occur in Indonesian society differently compared to other countries. Calcium intake is mainly from milk, with a calcium content in 100 grams of milk is 143 mg. The number of calcium adequacy recommended at the age above 30 years is 1000 mg. Almost all of our subjects drink milk every day.[6,12,13]

Characteristics of subjects seen from the osteoporosis group had an average age of 66.54±6.66 years, osteopenia with 64.50±6.45 years and normal subjects with 68.62±6.90 years. Further analysis revealed no significant correlation. This result is similar to the research conducted by Sabit et al, who found an average age of 65 years, as well as research by Dubois et al. and Dimai et al. In contrast to the study by Katsura et al, they found an average age of 72 years and Forli et al found an average age of 52 years. A majority of our subject are in the age group 65-75 years which is the mean age for the osteoporosis group, this is because most subjects only came for treatment if they had symptoms that interfere with their lives, and they rarely seek treatment on minor complaints.[7,9,14–16]

In the osteoporosis group, there were 9 males and 3 females, while in the non-osteporosis group all 20 of them were males. Analysis showed a significant relationship between sex with osteoporosis in stable COPD but

because this result does not reflect the actual population thus it cannot be taken as a conclusion of the study. Hattiholi et al also found a high prevalence of osteoporosis in the female population. Ferguson GT et al's study found that the prevalence of osteoporosis was high in COPD patients regardless of gender.[8,17]

The fact is that women are always in a high risk for osteoporosis idue to the effects of estrogen. Women with osteoporosis are strongly associated with menopause. At menopause, estrogen levels will decrease significantly, and estrogen is known to be important in regulating bone growth and homeostasis. Low esterogen results in an increased proliferation of osteoblasts and osteoclast apoptosis. Low esterogen also results in decreased calcium absorption and decreased calcium reabsorption in the kidneys, resulting in hypocalcaemia and increased parathyroid hormone. All of the above results in bone resorption in osteoporosis.

In this study, from the osteoporosis group there were 8 former smokers and 4 nonsmokers, while in the non-osteoporosis group there were 19 former smokers and 1 nonsmoker. Analysis found no significant association between smoking history with osteoporosis in stable COPD. Statistically there was no significant relationship, but when viewed from the percentage of osteoporosis groups, most of the osteoporosis patients had a history of smoking. Similar results from Silva et al's study showed no significant relationship between smoking and DMT.[18]

Smoking is included as an independent factor for osteoporosis, the mechanism related to smoking and osteoporosis is not clearly understood though it is assumed to be related to damage to the alveolar tissue and bone structures. The potential mechanism is through influencing the RANK-RANKL-OPG system. Smoking has a cumulative dose effect as an independent factor in DMT in the pelvic, vertebrae, lumbar and forearm bones.

This study obtained a history of corticosteroids in the osteoporosis group as many as 9 people using inhaled corticosteroids with a dose of Budesonide/formoterol (320 micrograms/day) and Salmeterol/ fluticasone (500 micrograms/day), and 3 people without corticosteroid usage. After analysis there was no significant relationship between the history of corticosteroids and osteoporosis in stable COPD.

This is in line with the research of Toward a Revolution in COPD Health (TORCH) which did not found a

significant effect on DMT examined from the placebo group and the group treated with inhaled corticosteroids 2 times a day for 3 years, in which DXA examined the lumboskaral and hip regions. DMT values in the placebo group were -3.1%, followed by groups of salmeterol 50 µg DMT -1.7%, fluticasone propionate 500 µg DMT -2.9% and a combination of salmeterol/fluticasone propionate 50 µg/500 µg DMT -3.2%.[8,17–19]

In contrast to the control study in 1780 COPD patients with non-vertebral fractures and 6817 subjects as controls, high doses of corticosteroids >700 µg/day were associated with increased fracture risk compared to subjects without inhaled corticosteroids (OR=1.68; 95% CI=1.10-2.57).[17]

Inhalation corticosteroids are often used in group C and D COPD patients to reduce the frequency of exacerbations and improve quality of life. Oral corticosteroids are used in patients with COPD exacerbations both outpatient and inpatient care with the aim of improving pulmonary function as early as possible. Corticosteroids appear to be independent risk factors for secondary osteoporosis. The fact is that osteoporosis can occur without a history of corticosteroid use. The risk of osteoporosis appears to increase along with the degree of severity, not only from inhaled corticosteroids. Corticosteroids interfere with osteoblast activity and increase osteoblast apoptosis through inhibition of the *Wnt/β-catenin signaling system* which is important for osteoblastogenesis.

This study obtained a median BMI of osteoporosis group subjects of 16.75 (14.0-25.2) kg/m^2 while the non-osteoporosis group of 23.20 (17.3-34.2) kg/m^2, after analysis a significant association between BMI and osteoporosis in stable COPD was found (P<0.001). The results of this study is similar with that obtained by Forli et al namely BMI of 19.0 kg/m^2 with a 48% prevalence of osteoporosis.[9] Sabit et al obtained lower results, in subjects with a BMI of 27.6 kg/m^2 they obtained an osteoporosis prevalence of 24%.[18]

Our results found that osteoporosis groups had a BMI that was low or thinner than the non-osteoporosis group. In contrast to Forli et al's research, although BMI is equally lacking, they have a higher prevalence of osteoporosis because the subjects had lower lung function. Low body mass index is a key risk factor for low DMT and compression fractures in the future while high BMI is a protective factor of osteoporosis. Fracture risk increased at BMI <25 kg/m^2, every 1 SD decrease in age-adjusted BMI increases the risk of fracture by 18%.

Weight loss or BMI is caused by IL-6 which stimulates CRP causing skeletal muscle weakness and TNF alpha causes cachexia, skeletal muscle weakness, increased metabolism, increased protein breakdown. This is a systemic manifestation of COPD characterized by elevated levels of IL-6, IL-8, CRP and TNF-α.

The 25-OHD levels were not much different between the osteoporosis group of 25.43±10.44 ng/ml and the non-osteoporosis group of 25.47±7.99 ng/ml, and after analysis there was no significant association between 25-OHD levels and osteoporosis in stable COPD. Most of the osteoporosis subjects have vitamin D deficiency. The study subjects with vitamin D deficiency are mostly found in the age of 65-75 years (60%), underweight (40%) or normal weight (40%), history of smoking (60%) and severe (60%) or moderate (30%) COPD.[19,20]

Similar results from in Forli et al's study of 46 COPD patients showed a majority of vitamin D deficiency at normal or underweight patients Janssens et al showed vitamin D deficiency in COPD was higher than smokers without COPD, namely 31% and 60%, which increases along the severity of COPD with 60% of severe COPD and 77% of very severe COPD.[9,19]

Vitamin D deficiency is commonly found in the elderly, associated with the risk of osteoporosis and fracture. Vitamin D deficiency is influenced by age, exposure to cigarette smoke, lack of sun exposure, increased vitamin D catabolism due to glucocorticoids, lack of intestinal absorption and poor activation of the liver and kidneys.[19]

Several studies have shown low intake of foods containing vitamin D in COPD patients, especially in the elderly. Vitamin D deficiency causes osteoporosis through a decrease in serum calcium levels which are compensated by an increase in the level of parathyroid hormone then will increase cortisol production. Cortisol increases RANK expression on osteoclast surfaces resulting in bone resorption.

This study obtained FEV_1% mean prediction of osteoporosis group subjects of 45.78±11.06% prediction while the non-osteoporosis group was 51.71±18.83% prediction, which after further analysis did not showed a significant relationship between FEV_1% predictions with osteoporosis in stable COPD. The results of FEV_1/FVC% predictions were not much different between the mean of osteoporosis group subjects of 53.17±10.06% prediction and non-osteoporosis group by 52.69±12.69% prediction, and after

analysis there was no significant association between FEV_1/FVC% predictions with osteoporosis in stable COPD.

This study found that the majority of osteoporosis group subjects had a lower FEV_1 level of moderate to severe GOLD criteria, which is in line with the assumption that the risk of osteoporosis increases with the severity of COPD.[21] The osteoporosis group is mostly in moderate-to-severe COPD degrees and in groups B and D that are often associated with the risk of exacerbations, causing the need of systemic corticosteroids.

Osteoporosis in COPD increases the risk of fracture, if there is a vertebral fracture then FEV_1 may be even lower. Osteoporosis therapy is needed to prevent further bone loss and reduce the risk of fracture due to osteoporosis. Most studies showed increased risk of osteoporosis in low FEV_1 . Jorgensen et al's study on the prevalence of osteoporosis in severe COPD (FEV_1<1300 ml, an average of 31.4±7.3% predictions) associated with glucocorticoid therapy in osteoporosis, found that 68% of subjects had osteoporosis or osteopenia, however, glucocorticoid usage alone cannot explain the increased prevalence of osteoporosis.[22]

In this study there are limitations including the low number of subjects, that we consider may not represent the female population. The study design was cross-sectional so it could not explain the exact results that showed a causal relationship due to osteoporosis in stable COPD. Statistically, there was a significant correlation between BMI as a risk factor for stable COPD but this result could not explain the causal relationship because this study could not know the cause, thus various additional studies and tests are still needed.

CONCLUSION

The prevalence of osteoporosis in stable COPD patients in RSUP Persahabatan Hospital is 37.5%. There were no significant correlation between the stable COPD group or group with osteoporosis as a comorbid factor , but osteoporosis appear as a comorbid factor in stable COPD patients even in group A and GOLD moderate-severe degree. There was no significant association between osteoporosis risk factors, such as gender, smoking history, corticosteroid history, age, 25-OHD level, FEV_1% prediction and FEV_1/FVC% predictions in stable COPD. A significant association between BMI as a risk factor for osteoporosis in stable COPD is found.

Suggestions from researchers is this research should be carried out with a case control design with a larger number of subjects comparing stable COPD patients with normal smokers and non-smoking patients so that the scores between the two can be obtained. Researcher recommend that stable COPD patients be screened early to detect risk factors for osteoporosis.

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ORIGINAL ARTICLE

The Proportion Of Lung Hyperinflation In Patients With Persistent Asthma In Persahabatan Hospital Jakarta Using Multiple Breath N_2-Washout

Marisa Afifudin, Faisal Yunus, Triya Damayanti

Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Indonesia - Persahabatan Hospital, Jakarta

ABSTRACT

Background: In asthma, small airway dysfunction and inflammation may induce significant lung hyperinflation. The aim of the study is to discover the proportion of lung hyperinflation in patient with persistent asthma in Persahabatan Hospital Jakarta.

Method: A cross sectional study with descriptive analysis was done in Asthma clinic Persahabatan Hospital from September-November 2016. Forty-five subjects were recruited consecutively. Interview, physical examination, chest x-ray (CXR), spirometry and multiple breath N_2-washout (MBW) were performed. Lung hyperinflation was defined as a residual volume /total lung capacity (RV/TLC%) above the upper limit of normal.

Results: The proportion of lung hyperinflation in patients with persistent asthma was 17,8% (8 of 45 subjects). Median RV in milliliter was 1230 (570-2860). Median functional residual capacity (FRC) in milliliter was 1730 (970-3990). Median TLC in milliliter was 3310 (2490-6350). Mean RV/TLC ratio was 36.39% (SD±8.86). Mean FRC/TLC ratio was 52.86% (SD±6.85). There was a significant correlation between forced expiratory volume in 1 second (FEV_1%) value with lung hyperinflation with the decline of FEV_1 <60% increased the risk of lung hyperinflation by 8,46 (95%CI=1.155-61.98; P=0.036). There were no significant correlation between age, gender, smoking habit, body mass index (BMI), ACT score, the severity of persistent asthma, duration of asthma, duration of steroid inhalation use, exacerbation history in the last 12-months and emphysematous in CXR with lung hyperinflation (P>0.05).

Conclusion: The proportion of lung hyperinflation in patient with persistent asthma in Persahabatan Hospital Jakarta is 17,8%. Lung hyperinflation in persistent asthma is associated with the degree of airway obstruction.

Keywords: lung hyperinflation, persistent asthma, multiple breath N_2-washout

*Correspondence: Triya Damayanti - tria_94@yahoo.com

Submitted: February 14th 2021, Accepted: February 27th 2021, Published: February 28th 2021

INTRODUCTION

Asthma is a disease characterized by an increase in airway reactivity. Patients with asthma have persistent or recurrent airflow obstruction, either reversible or spontaneously. The number of asthma patients around the world will increase by estimated 100 million in 2025. The cause of mortality due to asthma every year is estimated 250,000 people.[1]

At the household health survey, asthma, chronic bronchitis and emphysema as fourth or 5.6% cause of death (mortality) in Indonesia. In 1995, the prevalence of asthma throughout Indonesia amounting 13/1000, compared to chronic bronchitis 11/1000 and pulmonary obstruction 2/1000.[2]

Obstructive pattern is the most common pattern, identified through the decline of forced expiratory volume in 1-second (FEV_1) and FEV_1 ratio with forced vital capacity (FEV_1/FVC) or FEV_1/vital capacity (VC). Some patients may have a decreasing FVC from air trapping, result in pseudophysiologic emphysema in lung function test with increasing total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV).[3]

The present physiologic study evaluated patients with moderate to severe, chronic persistent asthma who have seemingly irreversible lung function despite aggressive treatment, to determine the mechanisms of airflow limitation. Physiologic consequences of loss of lung elastic recoil in chronic persistent asthma include hyperinflation, premature airway closure, and abnormal expiratory airflow.[4] It is widely known that patient with asthma chronic may develop some degree of hyperinflation which may persist after remission.[5]

Lung hyperinflation is probably one of the major causes of dyspnea in patients with asthma. Hyperinflation is a compensated mechanism as a response of the airway resistance. In routine clinical practice, hyperinflation is usually defined by an FRC above 120% of predicted, which is generally preceded by an elevation in RV and thus an increase in the ratio of RV to the TLC (RV/TLC).[4–6]

Study of lung hyperinflation in asthma patient in Indonesia had not been done yet, thus the authors aimed to discover the event of lung

hyperinflation in patient with persistent asthma. Lung function tests to determine lung hyperinflation can be done using body plethysmograph, gas dilution and washout. A nitrogen washout procedure can be performed with a single nitrogen breath washout (SBW) or multiple breath N_2 washout (MBW). MBW requires only passive cooperation and minimal coordination. In this study we were using MBW procedure.

The aim this study to discover the proportion of lung hyperinflation in patient with persistent asthma in Persahabatan Hospital Jakarta using multiple breath N_2-washout.

METHOD

A cross sectional study were done in Department of Pulmonology and Respiratory Medicine - Persahabatan Hospital Jakarta during September-November 2016. Inclusion criteria including patient diagnosed with persistent asthma based on medical record in Asthma Clinic Persahabatan Hospital Jakarta and willing to participate in the study. Exclusion criteria including patient with acute exacerbation or history of exacerbation four weeks prior accompanied by doctor visit, pregnancy, comorbidity such as active tuberculosis (TB) and history of TB, bronchiectasis, interstitial lung disease and malignancy, patient with life threatening infection, other fatal terminal disease and severe comorbid, lung parenchymal abnormality in CXR aside from emphysema and refused to participate.

Subjects were recruited consecutively. Interview, physical examination and vital signs were done in subjects who met the inclusion criteria. Afterwards, CXR were taken in subjects without CXR in the last one-month. Spirometry and MBW were perfomed using NDD EasyOne Pro®LAB. Washout was considered complete if N_2 concentration less than 2% in at least three consecutive breath. At least one measurement was technically acceptable.

FEV_1, VC and IC determined from spirometry result. FRC measurement done using MBW method. TLC value result from FRC + IC, then RV measurement taken from TLC minus VC. Hyperinflation was determined based on RV/TLC above the upper limit of normal. Data were analyzed using

Statistical Package for Social Science (SPSS) 21.

RESULT

We interviewed 72 subjects who meet with inclusion criteria. Forty-five subjects completed the study, while 11 subjects had exacerbation just before conducting lung function tests, 4 subjects with severe comorbidity were excluded (3 heart failures, 1 cirrhosis), 3 subjects with parenchymal abnormality aside from emphysema in CXR were also excluded (TB, bronchiectasis, lung edema) and 9 subjects were loss to follow-up.

Table 1. Demography characteristics

Characteristics		n	%
Gender	Male	9	20
	Female	36	80
Age (years)	Mean	50,38	SD±14,96
	<40	10	22,2
	40-60	22	48,9
	>60	13	28,9
Smoking habit	NonSmoker	38	84,4
	Ex-smoker	7	15,6
	Mild BI	0	0,0

Forty-five subjects including 9 males (20%) and 36 females (80%) were recruited. Mean age was 50,38 (SD±14,96). Subjects in age group 40-60 years old were dominant with 22 (48,9%). Seven subjects (15,6%) were ex-smokers with mild Brinkman index (BI), while 38 subjects (84,4%) were nonsmoker. There was no active smoker in our study. Demography characteristics as seen in Table 1.

Mean duration of asthma was 21,91 years (SD±16,45) with duration of asthma >20 years in 22 subjects (48,9%). Moderate persistent asthma was dominant group with 36 subjects (80,0%). Dominant BMI was obese I with 18 subjects (40,0%). Median ACT score was 20. Exacerbation in the last 12-months in 24 subjects (53,3%) while 21 (46,7%) subjects with no exaserbation history. Duration of steroid inhalation use <5 years was dominant with 26 subjects (57,8%). Emphysematous in CXR found in 6 subjects (13,3%) (Table 2).

Median FRC (in milliliter) was 1730 (970-3990). Median RV (in milliliter) was 1230 (570-2860). Median TLC (in milliliter) was 3310 (2490-6350). The complete spirometry and MBW results in Table 3.

Table 3. Spirometry and MBW test results

Category	Mean/ Median	Range
FEV_1 (ml)	1443,78	SD±437,41
FEV_1 (%)	75,02	SD±23,62
Air trapping (%)*	5,00	0-20
FRC (ml)*	1730	970-3990
RV (ml)*	1230	570-2860
TLC (ml)*	3310	2490-6350
RV/TLC (%)	36,39	SD ±8,86
FRC/TLC (%)	52,86	SD ±6,85

*distribution not normal

Table 2. Clinical characteristics

Characteristics		N	%
Duration of asthma (years)	Mean	21,91	SD ±16,45
	<10	13	28,9
	10-20	8	17,8
	>20	24	53,3
Severity of persistent asthma	Mild	7	15,6
	Moderate	36	80,0
	Severe	2	4,4
BMI	Underweight	2	4,4
	Normal	9	20,0
	Overweight	8	17,8
	Obesity I	18	40,0
	Obesity II	8	17,8
ACT score	Mean	20 3	6-25
	25	20	6,7
	20-24	22	44,4
	≤19		48,9
Exacerbation history (last 12-months)	Yes	24	53,3
	No	21	46,7
Duration of steroid inhalation	<5 years	26	57,8
	≥5 years	19	42,2
CXR	Emphysematous	6	13,3
	No emphysematous	39	86,7

Table 4. Correlation between demography characteristics with lung hyperinflation

Characteristics	Hyperinflation	No hyperinflation	P
Age			
≤50	6	15	0,083*
>50	2	22	
Gender			
Male	4	5	0,039*
Female	4	32	
Smoking habit			
Non-smoker	1	6	0,0637*
Ex-smoker	7	31	

Note: *Fisher test

Lung hyperinflation was determined based on RV/TLC above the upper limit of normal (RV/TLC>pred+1,64 residual standard deviation/RSD). Reference value of RV/TLC in adult male 14,0+0,39xA with RSD 5,46, whilst in adult female 19,0+0,34xA with RSD 5,83 (A: usia). Reference value of RV/TLC in children and adolescent 21,7 (RSD=5,7).[26,36,37] Lung hyperinflation was found in 8 (17,8%) patients.

Proportions in persistent asthma for hyperinflation group are 17,80% meanwhile no hyperinflation group are 82,20%.

Table 5. Correlation between clinical characteristics, CXR and FEV_1 with lung hyperinflation

Characteristics	Hyperinflation	No hyperinflation	P
Severity of persistent asthma			
Mild	1	6	0,637*
Moderate-severe	7	31	
ACT score			
<20	6	16	0,107*
≥20	2	21	
Duration of asthma			
<20 years	1	18	0,065*
≥20 years	7	19	
Duration of steroid inhalation			
<5 years	6	20	0,248*
≥5 years	2	17	
Exacerbation last 12-months			
Yes	5	19	0,431*
No	3	18	
BMI			
Underweight-normal	3	8	0,298*
Risk	5	29	
CXR			
Emphysematous	1	5	0,714*
No emphysematous	7	32	
FEV_1			
≥60%	3	30	0,022*
<60%	5	7	

*Fisher test

Table 6. Multivariate logistic regression analysis

Variable	OR	95% CI	P
ACT <20	7,87	0,74-52,63	0,088
Male	6,99	0,93-83,33	0,059
Steroid use <5 years	8,06	0,71-90,90	0,092
Decrease of FEV_1<60%	8,46	1,155-61,98	0,036

Tabel 4 shows demography characteristics of age, gender and smoking habit with lung hyperinflation. The bivariate analysis shows a significant correlation between gender and lung hyperinflation (P=0,039), nevertheless, in multivariate analysis afterwards shows no significant correlation.

Tabel 5 shows the correlation between clinical characteristics, CXR and FEV_1 with lung hyperinflation. In bivariate analysis, there was a significant correlation between FEV_1(%) and lung hyperinflation (P=0,022) with 5 (41,7%) subjects

had decline of FEV_1<60%. There were no significant correlation between BMI, ACT score, the severity of persistent asthma, duration of asthma, duration of steroid inhalation use, exacerbation history in the last 12 months and emphysematous in CXR with lung hyperinflation.

Afterwards, lung hyperinflation associated with age, gender, ACT score, duration of steroid inhalation use, duration of asthma and FEV_1 (P<0,25) were analyzed using backward stepwise logistic regression. There was a significant correlation between FEV1% value with lung hyperinflation with the decline of FEV_1 <60% increased the risk of lung hyperinflation by 8,46 in persistent asthma (95% CI=1.155-61.98; P=0.036). Table 6 shows the multivariate analysis between the variables.

DISCUSSION

Present results show that approximately 50% of patients with poorly controlled asthma or baseline dyspnea exhibit a significant resting hyperinflation and patients with hyperinflation had lower FEV_1 and FEV_1/FVC values, worse asthma control, and a longer history of asthma. These findings confirmed that subjects with chronic asthma often develop some degree of hyperinflation, which may persist in the periods between exacerbations in patients with insufficiently controlled asthma. It is generally accepted (but not definitively proven) that lung hyperinflation is mainly related to abnormalities in the distal airways.

Natsir et al study in Persahabatan Hospital with 31 mild asthma subjects (intermitten and mild persistent) and 29 severe asthma (moderate-severe persistent).[7] Subjects characteristics were relatively similar in gender dominated by female (mild asthma 90.3%, severe asthma 79.3%), non-smoker (mild asthma 96.8%, severe asthma 96.6%), ACT score 1-20 (severe asthma 51.7%) and last 12-months exacerbation history (severe asthma 58.6%). Characteristics were found different in BMI normal (mild asthma 38.7%, severe asthma 41.4%) and the severity of persistent asthma dominated by mild persistent asthma with 24 subjects.

Perez et al evaluated lung hyperinflation in 305 subjects with 287 uncontrolled asthma. Subjects

characteristics which relatively similar with our study were mean age 48.7 (SD±17) years, BMI obese (mean BMI 25.2; SD±4.5), mean duration of asthma is 18.4 (SD±18,3 years) and ex-smoker subjects (16.6%). Different characteristics were found in lower mean ACT score 14.1 (SD±4.1) and active smoker subjects (14.4%).[6]

Gelb and Zamel studied 18 adults with chronic persistent asthma and one year exacerbation history. Subjects characteristics which relatively similar with our study was mean age 59 (SD±15) years and different with our study in gender, mostly male (12 subjects).[4] Zwitserloot et al studied 32 children diagnosed with asthma with mean age of 11.3 (4,717,4) and 19 male subjects. Steroid inhalation use in 22 subjects, mean ACT in age group <12 yr (11 subjects) was 25, whilst group >12 yr (14 subjects) was 23.5. Classification according to GINA were controlled 14 (40.6%), partly controlled 13 (40.6%), uncontrolled 4 (12,5%) and 2 unknown.[8]

The determination of FEV_1% value was adjusted with predictive value of Indonesian people according to Indonesia Pneumobile Project 1992 calculation. The RV, FRC and TLC values were not presented in percent predicted because the predicted value adjusted to Indonesian people were not available and MBW tool providing only predicted value of South East Asian in general.

Natsir et al study found mean FEV_1% in mild asthma was 90,12% (SD±15,67) and in severe asthma was 56.82% (SD±14.35%). The FEV_1% difference with our study can be caused by differences in the distribution of asthma degree.[7] Perez et al evaluated patients with poor controlled and found mean FEV_1% 75.8% (SD±18.7%) which was similar to our study. Mean RV/TLC was 44.2% (SD±11.2%) which was relatively higher presumably because the study had bigger sample size and lower ACT score compared to our study.[6]

Gelb and Zamel in Los Angeles, USA and Ontario, Canada studied 18 adults with chronic persistent asthma, fixed expiratory airflow obstruction and one year exacerbation history; 12 men, six women, age 59±15 yr divided into 3 age groups and found the decrease of $FEV_1 \geq 1$. lt (>35% predicted value) compared to one year before. The FEV_1 value were lower

than our study presumably because of less subjects and age distribution, whilst FRC, RV and TLC values were higher compared to our study presumably because racial difference and the difference of methods.[4]

Bourdin et al using single breath N_2-washout (SBNT) in 24 asthmatics (13 females) of various severity but with normal FEV_1 were compared with 24 healthy volunteers (13 females) and studied at steady-state after bronchodilatation which was different from our study. The FEV_1, FRC, RV and TLC values were higher compared to our study presumably because racial differences, asthma subjects including mild degree and the difference of methods. Zwitserloot et al in study of 32 children diagnosed with asthma found the average FEV_1/prediction was 99.7% (SD±14.4%).[8,9]

Lung hyperinflation was determined based on RV/TLC above the upper limit of normal (RV/TLC>pred+1.64 RSD). Lung hyperinflation was found in 8 (17.8%) patients. Perez et al evaluated lung hyperinflation in poor controlled asthma (ACT<20). Hyperinflation was defined as either a RV/TLC above the upper limit of normal or a FRC>120% predicted. The prevalence of lung hyperinflation observed in 48% (146 dari 305) patients.[6] Jain et al in a recent observational study, 51% of patients with symptomatic or nonsymptomatic persistent asthma treated with a fixed ICS/LABA combination displayed lung hyperinflation.[10] Labbé et al studied 100 asthma children age 5-16 years old then evaluated hyperinflation based on high RV/TLC>30% and RV>120% and found 40 (40%) children with lung hyperinflation.[11] In 2013, Perez et al also investigated small airway disease in 222 subjects with stable asthma, moderate to severe and found 39% with lung hyperinflation based on high FRC>120%, RV>120% and RV/TLC>pred+1.64 RSD.[12]

Dykstra et al evaluated 4774 patients with obstructive lung diseases including 19% (908) subjects with asthma diagnosis based on history taking. The degree of hyperinflation, as determined by RV/TLC ratio, showed in 3% of asthma subjects or 0,64% higher among subjects with obstructive lung diseases. The different results compared with our study was presumed because of the

subject characteristic differences, Perez et al investigated poor controlled asthma with ACT<20, whereas Dykstra et al with asthma subjects regardless the degree of asthma severity. Another difference may be due to our sample size which were smaller.[6,13]

Backward stepwise logistic regression found that the decrease of FEV_1<60% has a strong correlation with the risk of lung hyperinflation in patient with persistent asthma by 8.46 (95% CI=1.155-61.98; P=0.036). This finding showed that subject with persistent asthma may develop some degree of hyperinflation and may persist in a period between exacerbations, influenced by the severity of airway obstruction. Dykstra et al[7] study showed strong correlation between lung hyperinflation based on RV/TLC with the degree of airway obstruction (FEV_1%). Perez et al also found strong correlation between FEV_1 value (mean 64.9% (SD±17.1), P<0.0001) with lung hyperinflation based on the incresing level RV/TLC.[6]

There were no significant correlation between age, gender, smoking habit, BMI, ACT score, the severity of persistent asthma, duration of asthma, duration of steroid inhalation use, exacerbation history in the last 12-months and emphysematous in CXR with lung hyperinflation. These findings are similar with Perez et al study in 2013 which found no significant correlation between age, gender, smoking habit, ACT score, duration of steroid inhalation use and exacerbation history in the last 12-months with small airway disease and in 2016 which also found no significant correlation between age, smoking habit, BMI, duration of asthma and exacerbation history with lung hyperinflation.[12]

Subjects were dominated by female because most outpatients in Asthma Clinic Persahabatan Hospital Jakarta are female. The determination of lung hyperinflation based on the increasing value of FRC was not assessed. There is no data of FRC predicted value tailored to the Indonesian people. Predicted value of RV and TLC for the Indonesian people were not exist as well so these percentage values were not calculated. This study did not use or compare with body plethysmograph which was more often used to measure and assess FRC value and lung hyperinflation.

Feasibility and overestimate results using body plethysmograph were among consideration.

CONCLUSION

The proportion of lung hyperinflation in patient with persistent asthma in Persahabatan Hospital Jakarta is 17,8%. Median RV in milliliter is 1230 (570-2860). Median FRC in milliliter is 1730 (970-3990). Median TLC in milliliter is 3310 (2490-6350). Mean RV/TLC ratio is 36,39% (SD±8,86). Mean FRC/TLC ratio is 52,86% (SD±6,85). There are no significant correlation between age, gender, smoking habit, BMI, ACT score, the severity of persistent asthma, duration of asthma, duration of steroid inhalation use and exacerbation history in the last 12-months with lung hyperinflation in patient with persistent asthma. There is a significant correlation between FEV_1% value with lung hyperinflation with the decline of FEV_1<60% increased the risk of lung hyperinflation by 8,46. Lung hyperinflation in persistent asthma is associated with the degree of airway obstruction. There is no significant correlation between emphysematous in CXR with lung hyperinflation in patient with persistent asthma.

Recommendations from researchers are further studies with healthy subjects as control, using other methods such as body plethysmograph, single breath N_2-washout and CT scan. Lung function test using multiple breath N_2washout as a routine test is recommended in patient with persistent asthma to assess lung hyperinflation, assist clinical decisions, thus improve hospital service. Further studies on normal value of residual volume, functional residual capacity and total lung volume based on age and height of Indonesian people such as Pneumobile Project 1992 are needed.

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