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Original Article

Correlation between Measurement of Lung Diffusion Capacity Using Single Breath Methods (D_{LCO}-SB) and COPD Group in Persahabatan Hospital Jakarta

Efriadi Ismail, Faisal Yunus, Triya Damayanti

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Abstract

Background: *This was a preliminary study to measure D_{LCO}-SB on COPD patients in Persahabatan Hospital to understand the prevalence of D_{LCO} reduction among COPD patients.*

Methods: *This was a cross sectional study of COPD patients who attended COPD-Asthma clinic in Persahabatan Hospital Jakarta. Spirometry and D_{LCO} -SB were performed consecutively during May–July 2015. Comorbidities were also recorded.*

Results: *Spirometry and D_{LCO} -SB measurements were conducted on 65 COPD subjects of which 10.8% subjects were in COPD Group A, 29.2% Group B, 32.3% Group C and 27.7% Group D. The mean age was 64.15; mean FEV_1% was 46.05%, mean D_{LCO} measured was 19.42 ml/min/mmHg and the mean D_{LCO} % was 72.00%. The proportion of D_{LCO} decline among COPD patients was 56.92%. There were significant correlations between COPD group, GOLD COPD grade, FEV_1, BMI and comorbidities with the D_{LCO} value results. There were no significant correlation between D_{LCO} value with sex, age, smoking history, Brinkmann Index, obstructive-restrictive criteria, comorbidities and length of COPD period.*

Conclusion: *The proportion of D_{LCO} decline among COPD patients was 56.92%. There were significant correlations between COPD group, GOLD COPD grade, FEV1, BMI and previous TB history with the results of D_{LCO}.* ***(J Respirol Indones 2021; 41(4): 260–71)***

Keywords: *spirometry, diffusion capacity of the lung for carbon monoxide (D_{LCO}), COPD, comorbidities*.

Hubungan antara Pemeriksaan Kapasitas Difusi Paru terhadap Karbon monoksida Metode Napas Tunggal (D_{LCO}-SB) dan Grup PPOK di RSUP Persahabatan Jakarta

Abstrak

Latar belakang: *Penelitian ini merupakan studi awal untuk mengukur D_{LCO} -SB pada pasien PPOK di RSUP Persahabatan Jakarta yang bertujuan mengetahui prevalens penurunan D_{LCO} pada pasien PPOK.*

Metode: *Penelitian ini menggunakan desain potong lintang pada pasien PPOK yang berkunjung ke Poliklinik Asma-PPOK RSUP Persahabatan Jakarta. Dilakukan uji spirometri dan D_{LCO} -SB pada pasien PPOK yang diambil secara berurutan antara bulan Mei-Juli 2015. Komorbiditas juga dicatat.*

Hasil: *Uji spirometri dan D_{LCO} -SB dilakukan pada 65 subjek yang terdiri dari 10,8% pasien PPOK Grup A, 29,2% Grup B, 2,3% Grup C dan 27,7% Grup Ddidapatkan rerata usia 64,15 tahun, rerata VEP_1% 46,05%, rerata nilai D_{LCO} 19,42 ml/menit/mmHg dan rerata D_{LCO} % sebesar 72,00%. Proporsi penurunan D_{LCO} pasien PPOK adalah 56,92%. Terdapat hubungan bermakna antara grup PPOK, derajat GOLD PPOK, VEP_1, IMT dan komorbiditas dengan nilai hasil uji D_{LCO}. Tidak terdapat hubungan bermakna antara nilai D_{LCO} dengan jenis kelamin, umur, riwayat merokok, Indeks Brinkmann, kriteria obstruksi-restriksi, komorbid dan lama terdiagnosis PPOK.*

Kesimpulan: *Proporsi penurunan nilai DLCO pada pasien PPOK adalah 56,92%. Terdapat hubungan bermakna antara grup PPOK, derajat GOLD PPOK, VEP_1, IMT dan riwayat TB dengan hasil uji D_{LCO}.* ***(J Respirol Indones 2021; 41(4): 260–71)***

Kata kunci: *spirometri, kapasitas difusi paru (D_{LCO}), PPOK, komorbiditas.*

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the non-communicable diseases which is a public health problem in Indonesia and was predicted to be the third cause of death in the world by 2020. Patients of COPD increase every year and as a cause, among other things, increased life expectancy and high exposure to risk factors. The host factor associated with the incidence of COPD cases is the increasing number of smokers (especially at young age) and also outdoor and indoor air pollution at work.[1,2]

Patients with moderate to severe COPD in Asia in 2006 had reached 56.6 million cases with a prevalence of 6.3%. The prevalence ranged from 3.5 to 6.7% as in China with COPD cases reaching 38.16 million, Japan had 5.014 million and Vietnam had 2.068 million cases. In Indonesia it was estimated at 4.8 million patients with a prevalence of 5.6%. At Persahabatan Hospital Jakarta, COPD patients increased from 616 in 2000 to 1735 in 2007.[3] These cases will increase in the future in line with the high smoking habits (men over 15 years 60–70%), population growth, increasing mean age of population, high burden industrialization, air pollution (especially in big cities, industrial and mining activities).[1–4]

COPD is a preventable and treatable lung disease, characterized by persistent airflow limitation which is usually progressive and associated with chronic inflammatory and respiratory responses to toxic/dangerous particles or gases. Exacerbations and comorbidities contribute to the severity of the disease.[1]

The characteristics of airway obstruction in COPD are caused by a combination of small airway obstruction (bronchiolitis obstruction) and various parenchymal damage (emphysema) in each individual.[1] Chronic inflammation causes changes in airway structure and narrowing in small airway. Pulmonary parenchymal destruction is also caused by an inflammatory process that results in damage to the wall of alveoli and reduces pulmonary elastic recoil so that these changes limit the ability of the airways to remain open during expiration. Airflow resistance can be assessed with spirometry devices that have been used throughout the world, in addition to be easily obtained and also reproducible in lung function test.[1,2]

Chronic inflammatory response induces parenchymal destruction leading to emphysema and disrupts normal repair mechanism and resilience of lung tissue resulting in small airway fibrosis. These pathological changes induce air trapping and progressive airway obstructions which lead to shortness of breath and typical COPD symptoms. Gas exchange from the alveoli to the capillary blood vessels can be estimated by measuring the capacity of the pulmonary diffusion of carbon monoxide (D_{LCO}). Decrease in D_{LCO} values can be due to the surface area of the alveolar-capillary gas exchange area, pulmonary capillary blood volume, membrane thickness and hemodynamic conditions such as cardiac output and hemoglobin levels. D_{LCO} is an examination to evaluate the severity of pulmonary fibrosis and pulmonary emphysema.[1,5]

Air trapping or residual volume deteriorates from the beginning of the COPD diagnosis so that the airway obstruction further worsens the pulmonary static hyperinflation. These changes can be measured by a body plethysmograph, or by measuring lung volume using helium dilution method but the accuracy is still below the body plethysmograph. D_{LCO} test with a single breath method provides information about the functional effects of emphysema in COPD and assists to explain the condition of patients with shortness of breath that is not in accordance with the degree of airway obstruction.[1,6–8]

This test is carried out to assess the estimated gas diffusion from the alveoli to pulmonary capillary vessels. Studies abroad found that D_{LCO} values were reduced in COPD patients and associated with decreased alveolar-capillary surfaces due to progression of pulmonary emphysema.[9,10] Deesomchok, et al.[10] obtained that 20% of grade 1 COPD patients had decreased D_{LCO} values below 70% of predictive value. Sin, et al.[10] found that 50% of grade 3 and 4 COPD patients had significant

decrease in D_{LCO} values. Another study found a significant positive correlation between the value of the first second forced expiratory volume (FEV_1) and D_{LCO} value. However, there were still no data about D_{LCO} test in COPD patients in Indonesia.[9–11]

This study aimed to determine the correlation between the D_{LCO} values using single breath method with the degree of COPD patients according to GOLD 2014.

METHOD

This cross-sectional study was conducted at Asthma-COPD Clinic of Persahabatan Hospital Jakarta during May to July 2015. Study subjects were all stable COPD patients who visited the Asthma-COPD Clinic in Persahabatan Hospital from May to July 2015. Primary data were obtained from interviews based on questionnaires while secondary data were gained from medical records of study subjects.

The sample size in this study was calculated based on the formula for cross sectional study. It was obtained as much as 60 subjects using consecutive sampling. Inclusion criteria were all stable COPD patients who visited the Asthma-COPD Clinic at the time of the study, and willing to sign informed consent after the full explanation of the study procedure. The exclusion criteria were COPD patients with comorbidities (such as diabetes mellitus (DM), interstitial lung disease (ILD), history of asthma, lung cancer and human immunodeficiency virus (HIV) infection) based on medical record data and COPD patients who were unable to complete spirometry examination and measurement of pulmonary diffusion capacity.

Study subjects will be interviewed and performed physical examination, spirometry and D_{LCO} test, examined for dyspnea score based on mMRC dyspnea score and COPD Assessment Test (CAT) and filled out study worksheet.

The research data were processed descriptively to see the frequency distribution of all observed variables, and bivariate analysis to see the correlation of each independent variable with the dependent variable observed followed by multivariate analysis if the requirements were fulfilled.

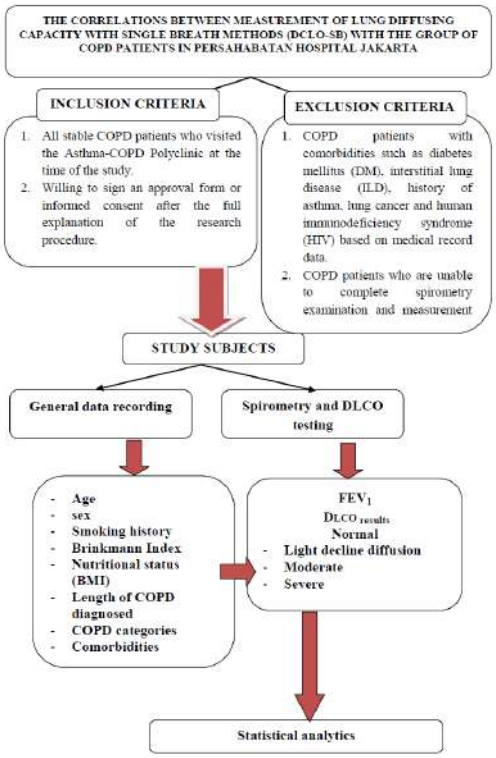

Figure 1. Study Pathway

RESULTS

The results of this study were primary data obtained from interviews, physical examination, spirometry examination and D_{LCO} test. A total of 65 subjects were consecutively collected and interviewed then spirometry and D_{LCO} tests were carried out.

Subjects consisted of 60 (92.3%) men and 5 (7.7%) women. Most subjects (39 subjects) were in the age range of 60-79 years. The highest level of education in the subjects was 27 (41.5%). There were 25 subjects who were still employed (38.5%) while those unemployed were 40 subjects (61.5%). Subjects who had smoking history were 56 subjects (86.2%) and 9 were non-smokers (13.8%). There were 55 subjects (84.6%) with moderate Brinkmann Index (BI) and 10 subjects (15.4%) with mild BI. Subjects diagnosed as COPD within less than or equal to 5 years were 57 subjects (87.7%) and who were more than 5 years were 8 subjects (12.3%). Based on the distribution of COPD group, the

subjects of COPD group A were 7 subjects (10.8%), group B of 19 subjects (29.2%), group C of 21 subjects (32.3%) and group D of 18 subjects (27.7%). If divided into COPD groups according to the latest GOLD criteria, group A-B COPD were 26 subjects (40%) and group C-D COPD were 39 subjects (60%). A total of 40 subjects (61.5%) with normal and lowest BMI were 2 subjects with obese. A total of 47 (27.3%) subjects had comorbidities while 18 (27.7%) subjects were without comorbidities. Subjects with former TB were 24 subjects (36.9%) and those without TB history were 41 subjects (63.1%). The characteristics distribution of subjects based on COPD groups spreaded mainly in COPD groups B, C and D. The complete subject characteristics can be seen in Table 1.

Table 1. Subject characteristic base on COPD group

Subject Characteristic	COPD Group				Total	%
	Group A	Group B	Group C	Group D		
Age						
40–59 years old	3	4	11	5	23	35.4
60–90 years old	4	15	10	13	42	64.6
Percents	10.8%	29.2%	32.3%	27.7%	100%	
Sex						
Male	7	18	18	17	60	92.3
Female	0	1	3	1	5	7.7
Education level						
Uneducated	1	2	0	1	4	6.2
Primary School	0	1	6	4	11	16.9
Junior High School	1	4	3	3	11	16.9
Senior High School	3	8	9	7	27	41.5
D3/S1 degree	2	4	3	3	12	18.5
Employment						
Employed	4	6	10	5	25	38.5
Unemployed	3	13	11	13	40	61.5
Smoking history						
Smokers	6	17	17	16	59	90.8
Non-smokers	1	2	4	2	6	9.2
BI (Brinkmann Index)						
Mild	1	2	4	3	10	15.4
Moderate	3	7	8	9	27	41.5
Severe	3	10	9	6	28	43.1
Length of time diagnosed as COPD						
0–5 years	6	14	20	17	57	87.7
≥5 years	1	5	1	1	8	12.3
BMI						
Malnutrition	1	1	5	5	12	18.5
Normal	6	13	9	10	38	58.4
Overweight	0	5	5	2	12	18.5
Obese	0	0	2	1	3	4.6
Spirometry test						
Obstructive	7	19	15	14	55	84.6
Mixed	0	0	6	4	10	15.4
Comorbidities						
Yes	3	12	16	16	47	72.3
No	4	7	5	2	18	27.7
TB history						
Yes	1	3	11	8	24	36.9
No	6	16	10	10	41	63.1
Total	7	19	21	18	65	100

Table 2. Mean value of spirometry and D_{LCO} test

Variable	Minimum	Maximum	Mean	SD
Age (year)	45	89	64.15	9.222
BMI (kg/m^2)	14	39	22.13	4.636
FEV_1(ml)	580	3160	1243.23	534.933
FEV_1 %	23	97	46.05	17.22682
FVC (ml)	1150	4520	2402.15	633.109
FVC %	34	98	68.23	14.90362
FEV_1/FVC%	35	104	66.40	16.28439
PEF (l/second)	1.61	9.82	4.31	1.50810
PEF %	25	109	59.61	19.48384
FEF_{25-75}	0.14	1.74	0.47	0.36140
FEF_{25-75} %	4	74	22.89	16.45555
D_{LCO} (ml/min/mmHg)	8.90	36.40	19.42	8.30442
D_{LCO}%	34	137	72.00	29.41817
VA(L)	2.58	7.43	4.49	1.15171
VA %	57	137	92.97	18.49828
KCO (ml/min/mmHg/L)	2.13	8.70	4.39	1.39650
KCO%	39	164	82.40	25.11586

Table 3. D_{LCO} value interpretations based on Degree of COPD and COPD group.

COPD Group	D_{LCO} Result (n)				Total	%
	Normal	Mild	Moderate	Severe		
COPD Group						
Group A	5	1	0	1	7	10.8
Group B	11	5	2	1	19	29.2
Group C	5	6	9	1	21	32.3
Group D	7	3	7	1	18	27.7
COPD degree						
GOLD 1	3	0	0	0	3	4.6
GOLD 2	13	6	4	2	25	38.5
GOLD 3	9	7	8	1	25	38.5
GOLD 4	3	2	6	1	12	18.5
Total	28 (43.07)	15 (23.07)	18 (27.69)	4 (6.15)	65	100

The mean age of the study subjects was 64.15 years (45–89). Mean BMI was 22.13 kg/m^2 (14–39). The mean FEV1% predictive value was 46.05% (23–97). The mean value of FEV_1/FVC was 66.40% (35–104). The mean D_{LCO} in ml/minute/mmHg was 19.42 (8.90-49.50). The mean D_{LCO}% predictive value was 72.00% (34–137). The mean value of KCO (D_{LCO}/VA) was 4.39 ml/minute/mmHg/L (2.13–8.70). The mean KCO% predicted was 82.4% (39–164). The characteristics of spirometry and D_{LCO} test results can be observed in Table 2.

Based on the interpretation of the D_{LCO} test according to the COPD degree of the latest GOLD criteria, the proportion of patients with D_{LCO} impairment was 37/65 (56.9%) while 28/65 (43.1%) had normal D_{LCO} values. Complete explanations were shown in Table 3.

If assessed by the degree of COPD according to spirometry criteria, in GOLD 1–2 COPD 16/28 subjects (57.1%) had normal D_{LCO} values, 6/28 subjects (21.4%) had mild decrease and 6/28 subjects (21.4%) had moderate decrease. Whereas in GOLD 3–4 COPD there were 12/28 subjects (42.9%) with normal D_{LCO} values, 6/28 subjects (21.4%) with mild decrease and 6/28 subjects (21.4%) with severe decrease. D_{LCO} The proportion of decreased D_{LCO} in group A-B were 10/26 subjects (38.5%) while in group C-D 27/39 subjects (69.2%). Bivariate analysis with chi-square test obtained *P* value of 0.014 (P<0.05). There was a significant correlation between COPD groups and decreased D_{LCO} values. The higher the COPD group (C-D) the greater the D_{LCO} decreased. More complete data are shown in Table 4.

Table 4. COPD group correlation with D_{LCO} results

COPD group	D_{LCO} results (n)		Total	%	*P*
	Normal	Decline			
Group A+B	16	10	26	40	0.014*
Group C+D	12	27	39	60	
Total	28	37	65	100	

Note: ***Chi-square test*

If the criteria of COPD group were divided into 4 main variables, which were GOLD degree based on spirometry, exacerbation history per year, breathlessness scale according to mMRC and CAT, it was found that spirometry had a significant correlation with decreased D_{LCO} (*P*=0.046) using bivariate analysis of Chi-square test. The proportion of D_{LCO} reduction in GOLD 1–2 was 12/28 subjects (42.9%) while in GOLD 3–4 was 25/37 subjects (67.6%) Higher degree of COPD had a decline in D_{LCO} value.

Table 5. Correlation of spirometry GOLD degree, CAT score, exacerbation and mMRC scale to D_{LCO} results

Categories	D_{LCO} results		Total	%	*P*
	Normal	Decline			
COPD degree					
GOLD 1–2	16	12	28	43.1	0.046*
GOLD 3–4	12	25	37	56.9	
mMRC scale					
mMRC 0–1	21	29	50	76.9	0.749*
mMRC ≥2	7	8	15	23.1	
Exacerbation history					
0–1 per year	24	35	59	90.8	0.221*
≥2 per year	4	2	6	9.2	
CAT score					
<10	9	19	28	43.1	0.121*
≥10	19	18	3	56.9	
Total	28	37	65	100	

Note: **Chi-square test*

When the FEV_1 value was divided into 2 categories; FEV_1 <1500 ml and ≥1500ml, in subjects with FEV_1 <1500 ml (49 subjects), the prevalence of D_{LCO} was about 33/49 subjects (67.3%) while insubjects with FEV_1 <1500 ml (16 subjects), the prevalence of D_{LCO} was about 4/16 subjects (25%). There was a significant correlation between the FEV_1 value and the D_{LCO} results. Subjects with FEV_1 <1500 ml experienced decrease in D_{LCO} values with *P* value of 0.004. The lower the FEV_1 value, the lower the D_{LCO} value.

Table 6. Correlation of FEV_1 values and DLCO results

FEV_1	D_{LCO} results (n)		Total	%	*P*
	Normal	Decline			
<1500 ml	16	33	49	75,4	0,004*
≥1500 ml	12	4	16	24,6	
Total	28	37	65	100	

Note: **Chi-square test*

Table 7. Factors that influenced the D_{LCO} results

Categories	D_{LCO} results		Total	*P*
	Normal	Decline		
Age group				
40–59 years	13	10	23	0.123*
60–90 years	15	27	42	
Sex				
Male	27	33	60	0.278*
Female	1	4	5	
Smoking History				
Smokers	24	32	56	0.602*
Non-smokers	4	5	9	
Brinkmann Index				
Mild	5	5	10	0.631*
Moderate-severe	23	32	55	
Obstruction Categories				
Obstructive	26	29	55	0.176*
Obstructive-restrictive	2	8	10	
Length of time diagnosed as COPD				
0–5 years	22	35	57	0.052*
≥5 years	6	2	8	
BMI				
Non-obese	16	34	50	**0.001***
Obese	12	3	15	
Comorbidities				
Yes	17	30	47	0.069*
No	11	7	18	
Total	28	37	65	

Note: **Chi-square test*

Of the several factors which affected the D_{LCO} values (sex, age, smoking history, BI, BMI, comorbidities, obstruction and length of COPD period), only BMI had a significant correlation with decreased D_{LCO} value (*P*<0.001).

It was found that 24 subjects (36.9%) were former TB and 41 subjects (63.1%) were not. COPD subjects with former TB experienced a decrease in D_{LCO} values compared with no TB history (*P*=0.037).

Table 8. Correlation of TB history with D_{LCO} results

TB history	D_{LCO} results (n)		Total	%	*P*
	Normal	Decline			
Yes	6	18	24	36.9	0.037*
No	22	19	41	63.1	
Total	28	37	65	100	

Note: **Chi-square test*

From bivariate analysis we found 5 variables with statistically significant correlation with decreased D_{LCO}, namely: FEV_1 value, COPD spirometry degree, COPD group, BMI and comorbidities. Afterward, we conducted a multivariate analysis using binary logistic regression method and received 2 variables with strong correlation to the D_{LCO} reduction, they were BMI with *P* value of 0.002 and FEV_1 with *P* value of 0.015.

Tabel 9. Multivariate Analysis (Binary logistic regression)

Variables	CI 95%	*P*
COPD group	0.362–2.291	0.240
COPD Degree	0.109–9.463	0.663
BMI	0.018–0.405	0.001
FEV_1	0.104–0.942	0.015
TB history	0.107–0.945	0.683

DISCUSSION

Subjects that was found the most in this study were in COPD group C (32.3%), followed by group B (29.2%). COPD patients often present with disturbing complaints so that patients start to look for treatment. Our study obtained subjects according to GOLD degree as GOLD 1 of 3 subjects (4.6%), GOLD 2 of 25 subjects (38.5%), GOLD 3 of 25 subjects (38.5%) and GOLD 4 of 12 subjects (18.5%). However, Boutou, et al. in their study that examined 604 COPD patients found GOLD 1 of 2.3%, GOLD 2 of 17%, GOLD 3 of 28.4% and GOLD 4 of 52.2%.[12]

Subjects in this study were 92.3% men and 7.7% women with mean age of 64 years, similar with study of Zhang, et al. in China on subjects with stable COPD that obtained mean age of 64 years among 89% men and 11% women.[13] Chugh, et al. in India gained a lower mean age of 61.50 years.[14] It was slightly different from previous local studies by Hanif and Hastuti with mean age of 67 years.[15,16] Miniati, et al. in Italy discovered mean age of 66 years among COPD patients. The highest age group in this study was more than 60 years, 64.4% of which was distributed in group B, C and D.[17] This was higher than study of Hanif that found 57.7% subjects in the age group >65 years.[15]

Moreover, Hastuti got higher subjects in the age group above 65 (71.1%).[16] This showed an increase in life expectancy and survival of COPD patients along with the quality improvement of the available health services. When viewed from the education level, secondary education (Junior High School and Senior High School) was the highest level of education (58.4%), the same result was observed in study by Hanif (57.8%) and Hastuti (57.9%).[15,16]

The number of patients diagnosed as COPD within 0–5 year reached 85.7%, this was because there were still many patients who routinely visited for regular control in the COPD clinic while those diagnosed above 5 years were 12.3%. This number was far less considering that COPD was progressively slow so that the COPD degree became heavier resulting in morbidity and mortality due to illness or other causes.

A total of 86.2% subjects had a previous smoking history. It was lower than study from Hanif (94.4%) and Hastuti (96%).[15,16] This stated that smoking was still the main cause of COPD in Indonesia. Only 13.8% of subjects who had no history of smoking in their lives were likely to become passive smokers or suffered from occupational COPD, related to the exposure to biomass. The severe BI in this study was 43.1%, almost similar to Hastuti (49.3%). Different result was seen in study from Hanif (56.71%). Miniati, et al. found an average BI index of 55%. These results supported smoking as a major risk factor for COPD.[17]

The mean BMI in this study was 22.13 kg/m^2 which was almost identical to study from Hanif that was 22 kg/m^2 and Hastuti 21 kg/m^2.[15,16] Andrianopoulous, et al. and Cassanova, et al. received higher result of 25.6 kg/m^2 and 28 kg/m^2, respectively.[18,19] These results indicated that the nutritional status of COPD patients in Europe was better than developing countries such as in Indonesia. In this study most subjects had normal BMI (61.5%), higher than Hanif (47.9%) and Hastuti (39.3%).[15,16]

We obtained 47 subjects (72.3%) with comorbidities which included mainly cardiovascular comorbidities (hypertension, heart failure and

ischemic cardiac history), while COPD subjects with previous TB history were 36.9%. Miniati, et al. also gained the same result of most comorbidity that was cardiovascular in as much as 95% subjects and the rest was other comorbidities. In this study there were 24 subjects (36.9%) with former TB while Miniati, et al. was 5%.[17] This might be due to Indonesia as the fourth highest country in TB cases in the world and the majority of TB patients also had smoking history. This was in contrast to European countries and other developed countries that had relatively small TB cases compared to degenerative and metabolic diseases.

We found mean FEV_1% predictive value of 46.05%, mean FEV_1/FVC of 66.40%, mean D_{LCO} result of 19.42 ml/minute/mmHg, mean D_{LCO}% predictive value of 72.00%, mean value of KCO (D_{LCO}/VA) of 4.39, and mean KCO% prediction of 82.4%. Sin, et al. studied 24 COPD patients in Ankara, Turkey in 2006 and found mean predicted FEV_1% of 43.79%, FVC% predicted value of 59.54%, FEV_1/FVC percent of 56%, D_{LCO} of 11.45 ml/minute/mmHg, D_{LCO}% predicted value of 49.16%, KCO of 3.13 ml/min/mmHg/L and KCO% (D_{LCO}/KCO) of 79.47.[10] Those numbers were lower than our study.

Gonzales-garcia, et al. in Bogota, Colombia on 2004 studied 25 COPD patients, 7 of them were women. They found out those subjects had moderate obstruction (43.3% VEP1) and moderate to severe D_{LCO}% 53.1% as much as 23%, FEV_1% predicted value of 43.3%, FEV_1/FVC of 44.7%, D_{LCO} of 14.68 ml/minute/mmHg, D_{LCO}% predicted value of 53.10, D_{LCO}/VA value of 3.20 ml/min/mmHg/L and predicted D_{LCO}/VA% of 65.7%.[20] Those numbers were also much lower than our study. Study from Boutou, et al. in Greece obtained FEV_1/FVC% prediction of 84.5% and mean D_{LCO}% prediction of 40.8%. The D_{LCO} value of COPD subject in this study was still higher than the results of study in Europe and South America.[12] This might be due to various subjects and there was a tendency to choose a subject that was truly able to complete the examination because the D_{LCO} test equipment could not be placed in clinic for safety reason.

Based on the interpretation of the D_{LCO} test in accordance with the COPD degree based on the latest GOLD criteria, the proportion of patients with a decrease in D_{LCO} values were 37 subjects (56.9%) while with normal D_{LCO} values were 28 subjects (43.1%). If the subjects were assessed by the degree of COPD according to spirometry criteria, in GOLD 1–2 COPD there were 16/28 subjects (57.1%) with normal D_{LCO} values and 12/28 subjects (42.8%) with decreased D_{LCO} values. Nevertheless, in GOLD 3–4 COPD there were 12/37 subjects (32.4%) with normal D_{LCO} values and 25/37 subjects (67.6%) with decreased D_{LCO}. The decreased D_{LCO} values in group A-B were observed in 10/26 subjects (38.5%) while in group C-D 27/39 subjects (69.2%). There was a significant correlation between COPD groups and decreased D_{LCO} values. There was a tendency of D_{LCO} value to decline in higher COPD group (C-D) with a *P* value of 0.014.

Foreign studies stated that D_{LCO} values decreased in COPD patients due to reduced alveolar-capillary surface caused by the development of pulmonary emphysema. Deesomchok, et al. discovered that 20% of patients with COPD grade 1 had decline in D_{LCO} values below 70% predictive value.[9] Fujimoto, et al. in 2011 found that COPD patients with emphysematous phenotype in inspiratory capacity and low D_{LCO} values showed greater dynamic hyperinflation compared to COPD patients with nonemphysematous phenotype.[21]

The decrease in pulmonary elastic recoil and alveolar bond due to alveolar destruction contributed significantly to the collapse of the alveoli and early airway closure during expiration (dynamic hyperinflation). Sariaydin, et al. stated that D_{LCO} values were reduced in emphysema patients in addition to the loss of alveolar-capillary surface area and heavy obstruction of the airway.[22] Sin, et al. in 2006 revealed that among 24 COPD patients, as many as 79% was proven to have parenchymal emphysema and about 50% had a decrease in D_{LCO} value.[10] Reduced D_{LCO} values might have a direct linkage to the loss of surface area of the alveolar capillary membrane due to emphysema. To assess

the level of emphysema, it was strongly recommended to conduct a High-Resolution Computed Tomography (HRCT) examination to determine the extent of the emphysema, and a D_{LCO} examination to confirm how much impairment in pulmonary diffusion capacity.

Of the four components that were elements to determine the distribution of COPD based on the group, the one that had a significant correlation with the D_{LCO} value was the degree of COPD based on spirometry with a *P* value of 0.046. The higher the degree of COPD, the more the tendency of decreased D_{LCO} value. Tanabe, et al. conducted a longitudinal study on the impact of COPD exacerbations on emphysema which resulted in exacerbations that caused the development of pulmonary emphysema in COPD patients. Emphysema progressiveness was also associated with a significant reduction in D_{LCO} values and should be evaluated as one of the considerations for COPD management.[23]

Lee. et al. in 2011 obtained 126 of 197 COPD patients were detected with emphysema while the rest 71 were non-emphysematous. They also found that COPD patients with emphysema had lower survival rates and higher rate of pulmonary loss.[24] Brusasco, et al. found that decline of D_{LCO} increased according to the degree of COPD. The D_{LCO} value started to decrease dramatically in GOLD 3–4. Decrease in D_{LCO} value compared to alveolar volume (D_{LCO}/VA) were seen in degree 1 because of early increase in VA and a tendency to increase to GOLD 4.[25]

In this study there was a significant correlation between the FEV_1 value and the D_{LCO} results. FEV_1 <1500 ml had more probability to have a decline in D_{LCO} values with *P* value of 0.004. The lower the FEV_1 value, the lower the D_{LCO} value. According to Brusasco, et al. the decreased D_{LCO} values in COPD patients usually occured after a decrease in FEV_1, so if D_{LCO} impairment was found to be severe but spirometry exhibited mild obstruction, another cause of D_{LCO} impairment should be considered.[25] Cystic fibrosis and alpha-1 antitrypsin enzyme deficiency should be considered in children and young adults with low obstruction and D_{LCO} values. This pattern was also seen in adult patients with bronchiolitis obliterans, bronchiectasis and lymphangioleiomyomatosis. The rate of decline in FEV_1 values could be predicted by the degree of obstruction and airway hyper reactivity. There was a little evidence that a decrease in D_{LCO} predictive values intensified mortality and morbidity in COPD patients (from baseline FEV_1 and airway hyper reactivity).[7,25]

Factors which influenced the results of D_{LCO} were: age, sex, smoking history, Brinkmann Index, obstruction category, duration of diagnosis of COPD, BMI category and comorbidities. After statistical analysis among factors which influenced D_{LCO}, BMI had a significant correlation with a decrease in D_{LCO} (*P*=0.001). The lower the BMI, the higher the risk of decrease in D_{LCO} value. Casanova, et al. revealed that the lower the BMI, the higher the risk of developing pulmonary hyperinflation which developed into emphysema.[3] The more severe the emphysema, the lower the D_{LCO} value. The age group of 60-90 years had a predisposition to decrease in D_{LCO} although it was not statistically significant (*P*=0.123). This could be due to the relatively small number of study subjects. Male sex was the majority subject in this study after statistic test pointed out a non-significant result and it was not related to a decrease in D_{LCO} value (*P*=0.278). From various studies, gender also did not have a significant correlation to the decline in D_{LCO} value.

In this study 57.1% of subjects with a history of smoking experienced a decrease in D_{LCO} values. It was statistically not found to be significant (*P*=0.075) but it clinically revealed that COPD patients with a smoking history would tend to experience a decrease in D_{LCO} values compared to those who did not smoke as smoking was the main risk factor for COPD. McCormack and colleagues stated that active smokers had lower D_{LCO} values which were more significant than non-smokers.[27] An important factor to be integrated into clinical interpretations such as when D_{LCO} went back to normal partially after quitting smoking, was to estimate the degree of D_{LCO} disorder due to

asbestos exposure. Decreased D_{LCO} in active smokers was not always associated with emphysema and could be affected by an increase in carboxyhemoglobin levels. However, the shortcoming in this study did not include hemoglobin examination as one of the factors which could influence the D_{LCO} results.

According to study from Mohammed, et al. in Iraq, it was observed that spirometry values such as FVC, FEV_1, FEV_1/FVC%, PEFR and D_{LCO} were found to be lower on smokers compared to non-smokers.[27] Han, et al. asserted that interference with diffusion capacity was a free predictor of emphysema tendency on radiological examination.[28] Patients with COPD usually present with comorbidities including cardiovascular, metabolic syndrome, osteoporosis, depression, reduction and periodic skeletal muscle dysfunction. The low long-term D_{LCO} value in active smokers with obstruction disorders is always associated with emphysema. D_{LCO} is an important index in assessing the anatomical degree of emphysema in smokers with airway obstruction. Low D_{LCO} values are highly correlated with the low mean lung density on CT-scans and in accordance with the anatomical degree of emphysema. Smokers with airway obstruction but normal D_{LCO} values usually have chronic bronchitis without emphysema. Patients with airway obstruction due to asthma can have normal or high D_{LCO} values.

We obtained 23 subjects (35.4%) with no TB history and 24 subjects (36.9%) who were former TB. Patients with comorbidities including TB experienced a higher decrease in D_{LCO} values compared to those without (*P*=0.047). Nevertheless, it could be questioned whether the subject possessed history of extensive TB lesions that might affect the results of D_{LCO}. Unfortunately, in this study there were no chest X-ray (CXR) examination to see the extent of TB lesions. However, spirometry in 7/24 (29.2%) COPD patients with former TB indicated obstruction and restriction. This evidenced that TB was one of the factors that worsened the decline in diffusion capacity among COPD patients in Indonesia.

Allwood, et al. from Cape Town, South Africa in 2014 examined the mechanism of airway obstruction in Tuberculosis-associated obstructive pulmonary disease (TOPD). They performed interview, spirometry, plethysmography, D_{LCO} tests as well as thoracic CT-scan on 196 subjects. They obtained 31 subjects (30.1%) without a history of TB, former probable TB of 39 subjects (33.32%), former definitive TB of 39 subjects (37.8%).[29] Subjects with a history of former definitive TB had a 16.3% lower D_{LCO} value (95%CI: -26.3–(-6.3%); *P*=0.002) than subjects without a history of TB. We also found that subjects with former TB had 6.5% higher experience of air trapping (*P*=0.014), 0.33% higher value of fibrosis score (*P*=0.007) and 3.5% higher emphysema score (*P*=0.038) than those without history of TB.

The mechanism of obstruction and decreased diffusion capacity in TOPD is narrowing of the airway due to bronchiolitis, bronchiectasis or persistent inflammation in consequence of the healing process of TB. Decreased elastic recoil corresponds to pre-existing emphysema. The term TOPD can be used as a separate clinical phenotype for COPD. COPD patients with a history of TB should be considered as one of the clinical phenotypes of COPD characterized by lower D_{LCO} values and more air trapping confirmed by pulmonary examination and CT scan.[29]

Of the 5 variables that correlated significantly with the decrease in D_{LCO} values when bivariate analysis was performed (FEV_1, COPD spirometry degree, COPD group, BMI and TB history), we conducted a multivariate analysis using binary logistic regression and obtained those variables which had strong correlation with D_{LCO} value reduction were BMI and FEV_1 with P values of 0.002 and 0.015, respectively.

There were some limitations in our study, included the subjects who were dominated mostly by male, no radiological examinations (CXR and/or thoracic CT scan) were performed, and no Hb level examination were carried out due to the limited funding.Further study is needed using homogenous

samples, control group as a comparison, CXR or thoracic CT examination, and Hb level examination.

CONCLUSION

The proportion of decreasing D_{LCO} values in COPD patients was 37/65 subjects (56.9%). The mean D_{LCO} value in COPD patients was 19.42 ml/minute/mmHg while the mean D_{LCO}% prediction was 72.00%, the mean FEV1% predictive value was 46.05%, the average FEV1/ FVC value was 66.40%. No significant relationship was found between demographic characteristics (sex and age) stable COPD patients with D_{LCO} test results. There is a tendency to decrease the value of D_{LCO} with the higher degree of COPD. There is a meaningful relationship between FEV_1 values and D_{LCO} values. VEP1 <1500 ml then the D_{LCO} value will decrease.

There is a significant relationship between BMI (nutritional status) and the value of D_{LCO}. the lower the IMT, the more D_{LCO} values will decrease. There is a tendency to decrease D_{LCO} values in COPD subjects with a history of smoking. There is no relationship between the duration of diagnosis of COPD and the value of D_{LCO}. Subjects with COPD with a history of former TB will have lower D_{LCO} values than COPD patients without prior TB history.

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