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Original Article

Accuracy of Inhaler Use in COPD Patients and Factors Affecting It

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Abstract

Background: An inhaler is a type of dosage form used in the treatment of chronic obstructive pulmonary disease (COPD). The inhaler has a unique technique for use; however, the percentage of accuracy in inhaler use is still low. Proper inhaler use is expected to improve quality of life and decrease the occurrence of exacerbations. This study aimed to observe the percentage of accuracy in using inhalers and the factors that influence it.

Method: This study was conducted with a cross-sectional design on COPD patients in two different hospitals. Primary data were collected using a questionnaire. The accuracy of inhaler use was assessed using a checklist.

Results: The total number of patients in this study was 110, with an average age of 62 years. Patients were given single inhaler therapy, which included Dry Powder Inhalers (DPI) for 34 patients with 70.7% accuracy, Pressurized Metered-Dose Inhalers (pMDI) for 9 persons with 45.74% accuracy, and Soft Mist Inhalers (SMI) for one person with 66.67% accuracy. Furthermore, patients who used a combination of pMDI and DPI inhalers had an accuracy value of 68.53%, while a combination of pMDI and SMI had an accuracy value of 72.72%. The stage with the lowest level of accuracy in the pMDI-type inhaler used alone was exhaling before the inhaler was supplied.

Conclusion: According to the findings, the accuracy of inhaler use in COPD patients is still relatively low. Furthermore, gender is a factor that has a statistically significant relationship with inhaler accuracy.

Keywords: COPD, DPI, inhaler technique, pMDI, SMI

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the three leading causes of death in the world. It is a common respiratory disorder characterized by persistent symptoms and airflow limitation due to exposure to harmful particles or gases. Treatment of stable or exacerbated COPD is carried out using an inhaler. Inhalers require specific techniques for use and are one of the causes of medication noncompliance.[1] Although inhalers are one of the best drug delivery devices, and previous study obtained that only 3% of patients found inhaler use difficult, half of these patients demonstrated incorrect inhaler use.[2]

In Indonesia, there are several types of inhalers in circulation with different drug formulations, such as Pressurized Metered-Dose Inhalers (pMDI), Dry Powder Inhalers (DPI), and Soft Mist Inhalers (SMI). All three types of inhalers are widely used by patients with COPD.[3] Unfortunately, only 2.86% of patients use the inhaler appropriately for all its stages.[4]

The Test of Adherence to Inhaler Toolkit has divided the causes of non-compliance by patients using inhalers into 3 categories, which include sporadic (reminders and counseling), deliberate (education and counseling), and unconscious (treatment plan and inhaler use instructions).[5] Inappropriate use of inhalers can lower disease control, increase drug consumption and side effects, increase the frequency of acute attacks or exacerbations, hospitalizations, drug expenses, and impair treatment success.[6]

According to one study, providing information on the inhaler use method reduced the frequency of moderate-to-severe yearly exacerbations and hospitalizations.[7] In this study, the accuracy of each stage of inhaler use in COPD patients was evaluated. We then assessed if any baseline patient characteristic influenced inhaler accuracy.

METHODS

A cross-sectional study was performed to examine the characteristics of COPD patients and assess the level of accuracy of inhaler use. The Universitas Indonesia Hospital Ethics Committee accepted this study under approval number S-049/KETLIT/RSUI/X/2022 with protocol number 2022-07-175. Consecutive sampling was conducted on COPD patients who underwent treatment control at Menteng Mitra Afia Hospital in November 2022, and at Grha Permata Ibu Hospital in December 2022. Sampling was terminated at the end of the sampling period.[8]

The inclusion criteria were patients diagnosed with COPD by a doctor, receiving at least one therapy administered in the form of an inhaler, and being willing to participate in the study as indicated by signing an informed consent. Patients with other chronic lung disorders, such as tuberculosis (TB) and pulmonary fungal infections, as well as those who were blind, deaf, speech-challenged, or illiterate, were excluded from this study. Demographic data from each patient was documented using a questionnaire regarding the patient's basic characteristics. The treatment data used was the treatment at the time the study was taken.

A different list was used for each type of inhaler circulated in Indonesia. Proper use of each step was scored separately. The checklist is from the NPS Medicine Wise Inhaler Technique: A device-specific checklist that has been adapted and used in the study of Sauriasari et al.[9] The list of steps to be performed is listed in Table 1. The accuracy score of inhaler use is defined as the percentage of correct steps compared to the total number of steps that should be executed. Patients who use combination inhalers demonstrated each inhaler separately.

Descriptive statistics were assessed with frequencies and percentages for qualitative variables and averages for quantitative variables. To see the correlation between two variables, the ANOVA test and the Pearson test were used. All analyses were performed using SPSS version 23. The value of $P<0.05$ was considered significant.

Table 1. Stages of inhaler use

Inhaler Type	Stages of Use
Diskus	1. Open the cap of the inhalation medication using your thumb.
	2. Hold the inhalation medication horizontally and set the dose by sliding the lever until it clicks.
	3. Exhale slowly and as fully as possible, away from the inhalation medication.
	4. Place the mouthpiece of the inhalation medication between the teeth without biting, and close the lips. Do not block the air outlet.
	5. Breathe in continuously and deeply.
	6. Hold your breath for 5 seconds or as long as possible (maximum 10 seconds).
	7. When holding your breath, remove the inhalation medication from your mouth.
	8. Exhale slowly, away from the inhalation medication.
	9. Close the inhalation medication after use.
	10. If the inhalation medication contains steroids, rinse your mouth with clean water after using the inhalation medication and do not swallow the remaining water.
Turbuhaler	1. Twist and remove the inhalation cap.
	2. Keep the inhalation medication in an upright position while turning the grip (red color) to the right.
	3. Turn the grip back the other way (toward the left) until it clicks.
	4. Exhale slowly, away from the inhalation medication.
	5. Place the inhalation mouthpiece between the teeth without biting, and close the lips. Do not block the air outlet.
	6. Breathe in strongly and deeply.
	7. Hold your breath for 5 seconds or as long as possible (maximum 10 seconds).
	8. When holding your breath, remove the inhalation medication from your mouth.
	9. Exhale slowly, keeping away from the inhalation medication.
	10. Close the inhalation medication after use.
	11. If the inhalation medication contains steroids, rinse your mouth with clean water after using the inhalation medication, and do not swallow the rinse.

Table 1. Stages of inhaler use (continue)

Inhaler Type	Stages of Use
PMDI	1. Unscrew the cap of the inhalation medication.
	2. Hold the inhalation medication in an upright position and shake it well.
	3. Exhale slowly, away from the inhalation medication.
	4. Place the inhalation medication between the teeth without biting, and keep the lips together
	5. Inhale slowly from the mouth, and at the same time, press the canister firmly.
	6. Continue to breathe in slowly and deeply.
	7. Then hold your breath for 5 seconds or as long as possible (maximum 10 seconds).
	8. While holding your breath, remove the inhalation medication from your mouth.
	9. Exhale slowly, away from the inhalation medication.
	10. Close the inhalation medication after use.
	11. If the inhalation medication contains steroids, you should rinse your mouth with clean water after using the inhalation medication, and do not swallow the remaining rinse water.
Breezhaler	1. Open the cap of the inhalation medication.
	2. Open the mouthpiece of the inhalation medication.
	3. Remove the capsule from the blister and place it in the capsule holder.
	4. Close the mouthpiece of the inhalation medication until it clicks.
	5. Press the right and left side buttons of the inhalation medication simultaneously and release (do not shake).
	6. Exhale one breath at a time.
	7. Place the mouthpiece of the inhalation medication between the teeth without biting, and keep the lips together.
	8. Breathe in strongly and deeply.
	9. Hold your breath for 5 seconds or as long as possible (maximum 10 seconds).
	10. While holding your breath, remove the inhalation medication from your mouth.
	11. Exhale slowly, away from the inhalation medication.
	12. Open the mouthpiece of the inhalation medication and take out the capsule. Check if it is empty.
	13. Close the inhalation medication after use.
	14. If the inhalation medication contains steroids, rinse your mouth with clean water after using the inhalation medication, and do not swallow the remaining rinse water.
Respimat	1. Hold the inhalation medication upright with the cap closed.
	2. Slide the bottom of the inhalation medication to the right (in the direction of the arrow) until it clicks (half a turn).
	3. Open the cap of the inhalation medication completely.
	4. Exhale slowly, away from the inhalation medication.
	5. Place the inhalation mouthpiece between the teeth without biting, and keep the lips together. Do not block the air outlet.
	6. Inhale slowly and deeply through the mouth, and at the same time, press the dose button.
	7. Continue to breathe in slowly and deeply.
	8. Hold the breath for 5 seconds or as long as possible (maximum 10 seconds).
	9. While holding your breath, remove the inhalation medication from your mouth.
	10. Exhale slowly, away from the inhalation medication.
	11. Close the inhalation medication after use.
	12. If the inhalation medication contains steroids, rinse your mouth with clean water after using the inhalation medication, and do not swallow the remaining rinse water.

RESULTS

This study included 110 patients with a mean age of 62 years, consisting of 32 female and 78 male patients. Only 20% (n=22) had a diploma or a university degree. The majority, 40% (n=44), had completed high school. About 76% (n=84) had a smoking history and had quit, but 11.82% (n=13) claimed to continue smoking. Table 2 shows detailed patient features.

As many as 35 patients were given only one type of inhaler, with four receiving only the reliever in the form of pMDI and 31 receiving both DPI and SMI controls. Twelve patients utilized a turbuhaler, sixteen used a diskus, two used a breezhaler, and one used a Respimat. A total of 75 individuals received more than one inhaler, with 72 receiving a combination of pMDI and DPI, and three receiving a combination of pMDI and SMI. Table 2 contains more complete information.

Table 2. Distribution of disease status and treatment-related factors in patients using different devices

Characteristic	Inhaler					*P*
	DPI	pMDI	pMDI + DPI	pMDI + SMI	SMI	
Gender						
Male	18 (23.08%)	7 (8.97%)	50 (64.10%)	2 (2.56%)	1 (1.28%)	0.086[a]
Female	16 (50.00%)	2 (6.25%)	13 (40.63%)	1 (3.13%)	0 (0.00%)	
Age (mean)	60.17	63.67	62.7	70.67	77	0.162[b]
Age range						
19–44	1 (25.00%)	0 (0.00%)	3 (75.00%)	0 (0.00%)	0 (0.00%)	
45–59	9 (39.13%)	0 (0.00%)	14 (60.87%)	0 (0.00%)	0 (0.00%)	0.735[a]
>60	24 (28.92%)	9 (10.84%)	46 (55.42%)	3 (3.61%)	1 (1.20%)	
Education						
Elementary school	9 (36.00%)	1 (4.00%)	14 (56.00%)	1 (4.00%)	0 (0.00%)	
Middle school	5 (26.32%)	2 (10.53%)	11 (57.89%)	1 (5.26%)	0 (0.00%)	0.570[a]
High school	13 (29.55%)	6 (13.64%)	25 (56.82%)	0 (0.00%)	0 (0.00%)	
College/university	7 (31.82%)	0 (0.00%)	13 (59.09%)	1 (4.55%)	1 (4.55%)	
Working						
Employe	11 (34.38%)	1 (3.13%)	18 (56.25%)	2 (6.25%)	0 (0.00%)	0.398[a]
Unemployed	23 (29.49%)	8 (10.26%)	45 (57.69%)	1 (1.28%)	1 (1.28%)	
Smoking status						
Non-smoker	5 (38.46%)	0 (0.00%)	8 (61.54%)	0 (0.00%)	0 (0.00%)	
Passive smoker	5 (71.43%)	1 (14.29%)	1 (14.28%)	0 (0.00%)	0 (0.00%)	0.265[a]
Ex-smoker	23 (27.38%)	6 (7.14%)	51 (60.71%)	3 (3.57%)	1 (1.19%)	
Current smoker	1 (16.67%)	2 (33.33%)	3 (50.00%)	0 (0.00%)	0 (0.00%)	
Comorbid						
With comorbid	21 (32.81%)	6 (9.38%)	34 (53.13%)	2 (3.13%)	1 (1.56%)	0.788[a]
Without comorbid	13 (28.26%)	3 (6.52%)	29 (63.04%)	1 (2.17%)	0 (0.00%)	
Therapy						
Reliever	2 (50.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Controller	32 (91.43%)	2 (5.71%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	<0.001[a]
Reliever and controller	0 (0.00%)	5 (7.04%)	63 (88.73%)	3 (4.23%)	0 (0.00%)	
No. of inhaler						
1	31 (88.57%)	3 (8.57%)	0 (0.00%)	0 (0.00%)	1 (2.86%)	
2	3 (4.35%)	6 (8.69%)	57 (82.61%)	3 (4.35%)	0 (0.00%)	<0.001[a]
3	0 (0.00%)	0 (0.00%)	6 (100.00%)	0 (0.00%)	0 (0.00%)	
Education history						
Literate	21 (26.92%)	5 (6.41%)	48 (61.54%)	3 (3.85%)	1 (1.28%)	0.298[a]
Illiterate	13 (40.63%)	4 (12.50%)	15 (46.88%)	0 (0.00%)	0 (0.00%)	

Note: [a]Pearson chi-square test; [B]ANOVA test

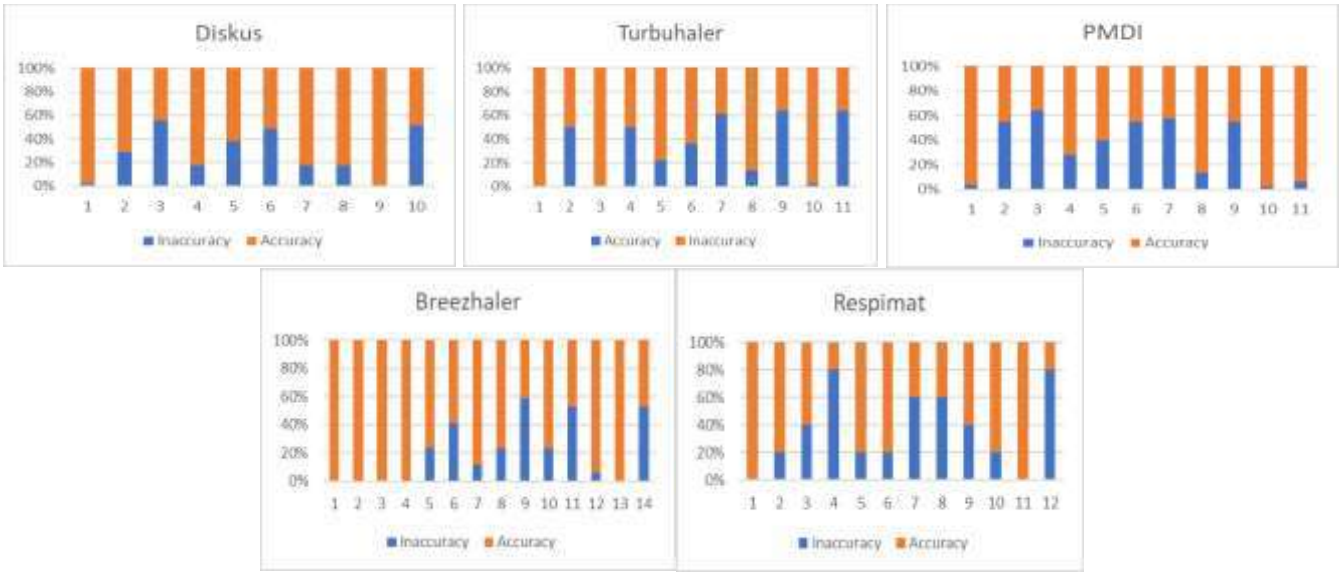

Figure 1. Percentage of inaccuracies committed by patients for each inhaler use

Table 3. Relationship between each variable and the percentage accuracy of inhaler use

Variable	Average of Accuracy	*P*
Gender		
Male (n=78)	64.87%	0.046[a]
Female (n=32)	73.38%	
BMI		
<18.5 (n=24)	62.50%	
18.6-24.9 (n=46)	64.33%	0.063[b]
25-29.9 (n=27)	74.85%	
>30 (n=13)	71.38%	
Age		
19-44 (n=4)	67.00%	
45-59 (n=23)	71.04%	0.572[b]
>60 (n=83)	66.34%	
Smoking		
Current smoker (n=6)	63.83%	
Ex-smoker (n=84)	65.94%	0.160[b]
Passive smoker (n=7)	83.57%	
Non-smoker (n=13)	69.31%	
Education		
Elementary school (n=25)	62.88%	
Middle school (n=19)	70.58%	0.063[b]
High school (n=44)	64.05%	
College/University (n=22)	76.23%	
Therapy		
Reliever (n=4)	50.00%	
Controller (n=35)	70.40%	0.135[b]
Reliever and controller (n=71)	66.82%	
No. of inhaler		
1 (n=35)	69.77%	
2 (n=69)	65.30%	0.295 [b]
3 (n=6)	76.67%	
Education History		
Literate	69.11%	0.147[a]
Illiterate	63.36%	

Note: BMI=Body Mass Index; [a]Mann-Whitney test, [b]Kruskal-Walis test

Five patients utilized the inhaler correctly at all stages. The highest percentage of inhaler accuracy was 79% in patients using Breezhaler-type inhalers, followed by 69.15% in patients using Diskus-type inhalers. Figure 1 depicts specific problems in inhaler use techniques.

Table 4. Percentage of accuracy of inhaler use for each inhaler combination

Inhaler	Accuracy
DPI (n=34)	70.70%
pMDI (n=9)	45.74%
pMDI + DPI (n=63)	68.35%
pMDI + SMI (n=3)	72.72%
SMI (n=1)	66.67%
Total (n=110)	68.54%

Note: pMDI=Pressurized metered-dose inhalers; DPI=Dry Powder Inhalers; SMI=Soft Mist Inhalers

DISCUSSION

This study evaluated the accuracy of inhaler use and the factors that influence it and found that the accuracy of inhaler use was 68.54%. Gender was a factor that showed a statistically significant relationship with the level of accuracy in using inhalers. This is important because identifying and characterizing incorrect inhaler use is the first step to determining the next intervention to improve inhaler use techniques.[10]

The accuracy of inhaler use in this study is close to previous studies, which stated that the error rate of inhaler use reached 25.3%.[11] Based on the combination of inhalers used by each patient, a more detailed level of accuracy can be shown. Table 4 shows the accuracy value for each combination of inhalers used, with the lowest accuracy value occurring in patients who use a single pMDI-type inhaler, with an accuracy level of only 45.74%. This is consistent with a prior study, which obtained that the level of inaccuracy in the usage of pMDI-type inhalers was 38.9% and pMDI combined with a spacer was 42.3 %.[4]

Similar to diskus and Respimat-type inhalers, the lowest percentage appears in the stage of slowly exhaling before administering the inhaler, which was 36 % in the pMDI type, 44% in the Diskus-type inhaler, and 20% in the Respimat-type inhaler. The stage of holding one's breath after spraying the inhaler had the second lowest accuracy rate in pMDI, Turbuhaler, and Respimat-type inhalers, with 42.67%, 39%, and 40%, respectively. Both stages are crucial in the use of pMDI, which has a consistently low percentage of accuracy.[12,13]

According to another study, the most common errors were not exhaling before using the inhaler, breathing through the nose, and not retaining the breath.[11] Breathing is typically more difficult to coordinate than other processes such as opening the cap or rotating the inhaler, especially in individuals with coughs or dyspnea.[14] Furthermore, if the inhalation medication contained steroids, the gargling step in Diskus, Turbuhaler, Breezhaler, and Respimat-type inhalers was frequently overlooked.

Patients did not rinse their mouth after using steroid-containing inhalers because they were unaware of the benefits and significance of this step, which was consistent with previous research.[15] Each type of inhaler has stages that are risk factors for errors in their use.[16] Details of the accuracy for each stage of inhaler use can be seen in Figure 1.

In addition to analyzing inhaler accuracy, this study looked at the presence or absence of basic patient characteristics that influence inhaler accuracy. Table 3 shows that age, smoking history, education history, type of therapy, and quantity of inhalers used do not have a statistically significant link with inhaler accuracy. Furthermore, there was a statistically significant relationship between gender and inhaler accuracy. Inconsistent findings have been found in studies on the relationship between gender and inhaler accuracy.[17]

Similar to other studies, this one showed that the accuracy of inhaler use in men was lower than in women.[12] However, some studies state otherwise, and other studies say there is no significant relationship between gender and the accuracy of inhaler use.[4,14,18] In addition, this study showed that BMI had no significant relationship with inhaler accuracy. However, other studies have suggested that BMI is closely related to COPD risk factors.[19]

The GOLD 2022 stated that smoking habits, adherence levels, and inhaler use techniques are influential in COPD management.[20] Six patients in this study still smoked. Although there was no statistically significant relationship between smoking habits and inhaler accuracy, the group that still smoked had the lowest inhaler accuracy of the other groups, at 63.83%. Furthermore, smoking is linked to risk factors and clinical conditions because it raises oxidative stress levels in the body, which are highly reactive to inflammatory cells.[21,22] Therefore, smoking can cause exacerbations in COPD patients.[22]

This study did not show a statistically significant relationship between the accuracy of inhaler use and education level. However, in another study, it was mentioned that patients with higher basic education would have a better understanding of the disease and the therapy.[23] It was found that the level of education affects the patient's level of understanding at each stage of inhaler use. In addition, patients with lower levels of education tended to make mistakes at critical points in the use of inhalers.[13]

The correct use of inhalers is an important point in COPD therapy because it will affect the number of doses administered and the effectiveness of treatment. Health workers need to understand the types of inhalers that can be used well by individual patients and emphasize important steps in their use.[15] Repeated demonstrations of inhaler use through various supporting media will be highly effective in reducing incorrect inhaler use, which will manifest in treatment effectiveness.[14,24] The absence of a significant relationship between the history of education and the accuracy of using inhalers indicates that there is a need for repeated education of COPD patients regarding their treatment.[4]

LIMITATION

There are several limitations to this study. First, there was no information on how long the patient used the inhaler, so the correlation with inhaler accuracy could not be determined. Second, we did not gather data on the incidence of exacerbations, so we cannot determine whether inhaler misuse affects the incidence of exacerbations. And third, we did not do proportional sampling, so the number of samples in each group was different. If further research is carried out based on the inhalers used, proportional sampling can be carried out so that each inhaler group has the same number of samples.

CONCLUSION

The study found that inhaler accuracy in COPD patients was still relatively low, with a total accuracy of only 68.54%. Furthermore, this study found that gender and BMI are factors that have a statistically significant relationship with inhaler accuracy. However, more research is required. Understanding

the sort of inhaler that can be used appropriately for each patient, offering instruction on inhaler use procedures, and validating the patient's abilities are all key aspects of treatment.

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CONFLICT OF INTEREST

This research has no conflict of interest.

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Original Article

Associations Between Measurement RV, RV/TLC, and FRC/TLC with Clinical Symptoms in COPD Patients in Persahabatan Hospital

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Abstract

Background: This preliminary study to measure lung volume in patients with stable COPD in Persahabatan Central General Hospital Jakarta to determine the prevalence of the increasing value of lung volume in patients with stable COPD.

Methods: This study used a cross-sectional study design of outpatients with stable COPD who visited the asthma-COPD clinic at Persahabatan Central General Hospital Jakarta. The Lung volume test using a gas dilution Multiple Breath Nitrogen Washout (MBNW) was taken consecutively from February to March 2016.

Results: Tests of spirometry and Lung volumes were performed on 35 subjects. There were 3 subjects (8.6%) in COPD Group A, 9 subjects (25.7%) in COPD Group B, 9 subjects (25.7%) in COPD Group C, and 14 subjects (40%) in COPD Group D. At the age of 60 years, there were subjects (25.7%) and 60 years, 26 subjects (74.6%). Value Residual Volume/Total Lung Capacity (RV/TLC) has a significant relationship with the symptoms and a 6-minute walking test; however, Functional Residual Capacity/Total Lung Capacity (FRC/TLC) is significantly associated with the symptoms, a 6-minute walking test, and exacerbations within one year.

Conclusion: Value RV/TLC has a significant relationship with the symptoms and a 6-minute walking test; however, FRC/TLC is significantly associated with the symptoms, a 6-minute walking test, and exacerbations within one year.

Keywords: COPD, FRC/TLC, residual volume (RV), RV/TLC

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a chronic, progressive disease characterized by airflow obstruction that has no real change in its course. According to the 2014 Global Chronic Obstructive Lung Disease (GOLD) Report, COPD is a preventable and treatable lung disease characterized by persistent airflow barriers that are usually progressive and are associated with chronic inflammatory and respiratory tract responses to toxic or dangerous particles or gases. Exacerbations and comorbidities contribute to the disease severity.[1,2]

Changes in COPD pathology are complex and are associated with worsening respiratory physiology. Distal airways experience inflammation, airway wall fibrosis, smooth muscle hypertrophy, goblet cell hyperinflation, mucus hypersecretion, and pulmonary parenchymal destruction. The volume and number of submucosal glands and goblet cells increase, which results in chronic mucus hypersecretion in chronic bronchitis. In emphysema, the widening of the airways persists distally to the terminal bronchioles due to damage to the airway wall without fibrosis.[3,4]

Pulmonary function measurement has an important role in helping with the diagnosis and management of patients with respiratory disease. Pulmonary function tests that are often used are spirometry, Diffuse Lung Capacity (DLCO), lung volume, respiratory muscle strength, and the bronchial provocation test. Lung volume testing is mandatory to diagnose, manage, and prognosticate COPD. The importance of this test was shown by one of the studies by Talag et al, that for COPD patients who experience hyperinflation, it is necessary to have investigations such as spirometry or other static volume tests.[5]

However, it is different from the results of a study by Dykstra et al, who performed lung volume

examinations in 4,774 patients with obstructive pulmonary disease and found that there was little correlation between static volume and clinical symptoms.[6] But in Indonesia, there is no research data on the static volume test in clinical COPD patients. This study measures the relationship between RV, RV/TLC ratio, and the ratio of FRC/TLC to clinical symptoms in patients with stable COPD with influencing factors.

METHODS

This is a cross-sectional study of COPD-asthma outpatients in Persahabatan National Respiratory Referral Hospital using consecutive sampling. Inclusion criteria are all stable COPD outpatients in Asthma-COPD clinic willingly signed the informed consent form after a full explanation of the research procedure. Exclusion criteria are COPD patients suspected of having an acute pulmonary infectious disease characterized by the addition of symptoms of shortness of breath, sputum, and sputum discoloration; patients suffering from life-threatening infections; fatal terminal diseases; severe underlying diseases, including immunocompromise; COPD patients who are unable to complete a spirometry examination and measurement of lung volume; and former TB patients.

The latest chest X-ray was not performed; After anamnesis and physical examination, eligible subjects will be tested for spirometry and RV tests. FRC and TLC are calculated as tight scores based on mMRC and filled-out research worksheets. Recording of required data: general records, which include gender, age, smoking history, and the Brinkman Index. Record of measurements of the Body Mass Index, tightness score based on the criteria of the mMRC, 6-minute walking test, and exacerbation in the previous year.

RESULTS

The objectives of this study is to find the relationship between RV, RV/TTLC ratio, and the ratio of FRC/TTLC in asthma-COPD policlinic outpatient with clinical symptoms. The results of this study are based on primary data obtained from interviews, physical examinations, spirometry examinations, and lung volume tests. A total of 36 consecutive subjects were collected and interviewed, followed by a spirometry examination and lung volume test.

Table 1. Characteristics Of Research Subjects

Subject characteristics	N	%
Gender		
Man	35	100.0
Women	0	0.0
Age		
<60 years	9	25.7
≥60 years	26	74.3
History of COPD		
<5 years	28	80.0
≥5 years	7	20.0
COPD group		
Group A	3	8.6
Group B	9	25.7
Group C	9	25.7
Group D	14	40.0
Body Mass Index (BMI)		
Malnutrition	4	11.4
Normal	15	42.9
More nutrition	8	22.9
Obese	8	22.9
mMRC		
<2	10	28.6
≥2	25	71.4
Six-minute walking test		
>350	9	25.7
250-350	19	54.3
150-250	7	20.0
<150	0	0.0
Exacerbation		
<2	13	37.1
≥2	22	62.9
Smoking history		
Non-smoker	0	0.0
Former smoker	35	100
Brinkman Index		
Non-smoker	0	0.0
Mild	1	2.9
Moderate	20	57.1
Heavy	14	40.0
Symptoms		
Dyspnea	26	74.3
Chronic cough	9	25.7
Comorbid		
Without comorbid	16	45.7
With comorbid	19	54.4

A total of 35 study subjects consisted of 100% men. Subjects aged more than or equal to 60 years (74.3%) are the most common. Subjects who were diagnosed with COPD less than 5 years were 80.0% of subjects. COPD was divided into groups according the the latest GOLD criteria, Group A-B COPD was 34.3% and Group C-D COPD was 65.7%. As many as 42.9% of subjects with a normal BMI have the highest BMI.

The highest Modified Medical Research Council (MmRC) value is more or less equal to 2 or as much as 71.4%. The most successful six-minute walking test was at a distance of 250–350 meters by 54.3%. The history of exacerbations is more than or equal to 2 as many as 62.9% of subjects and exacerbations of less than 2 as many as 37.1%. The smoking history of the former smoker subject was 100.0%. Most subjects were moderate smokers about 57.1%, and 40% were heavy smokers. The most common symptoms are shortness of breath (74.3%) and chronic cough (25.7%). Most subjects in this studies have comorbidities (54.4%).

Table 2 shows the relationship between lung functions. There is no significant correlations between FEV_1 with RV, RV/TLC and FRC/TLC. The RV values that are smaller, RV/TLC and FRC/TLC are found in degrees III–IV compared to degrees I–II.

Table 2. The Relationship Between RV, RV/TLC and FRC/TLC Values with FEV_1 Values In Stable COPD Patients.

Category	FEV_1		Total (%)	*P*
	I-II (%)	III-IV (%)		
RV				
Normal	17 (51.5%)	16 (48.5%)	33 (100.0%)	0.227
Increase	2 (100.0%)	0 (0.0%)	2 (100.0%)	
RV/TLC				
Normal	1 (100.0%)	0 (0.0%)	1 (100.0%)	0.549
Increase	18 (52.9%)	16 (47.1%)	34 (100.0%)	
FRC/TLC				
Normal	9 (60.0%)	6 (40.0%)	15 (100.0%)	0.193
Increase	10 (50.0%)	10 (50.0%)	20 (100.0%)	

Table 3 shows the relationship between RV values, RV/TLC and FRC/TLC with clinical symptoms. There is no significant correlations between clinical symptoms and RV values. Increased RV values are found in symptoms of tightness. The value of RV/TLC when compared to clinical symptoms shows a significant relationship. The value of RV/TLC increased more in the symptoms of shortness of breath compared to symptoms of cough by 73.5%. There is a significant correlation between FRC/TLC with clinical symptoms. In shortness of breath, 85.0% increased FRC/TLC.

Table 3. The Relationship Between RV Values, RV/TLC and FRC/TLC With Clinical Symptoms in Stable COPD Patients.

Category	Symptoms		Total	*P*
	Cough	Dyspnoea		
RV				
Normal	9 (27.3%)	24 (72.7%)	33 (100.0%)	0.073
Increase	0 (0.0%)	2 (100.0%)	2 (100.0%)	
RV/TLC				
Normal	0 (0.0%)	1 (100.0%)	1 (100.0%)	0.030
Increase	9 (26.5%)	25 (73.5%)	34 (100.0%)	
FRC/TLC				
Normal	6 (40.0%)	9 (60.0%)	15 (100.0%)	0.001
Increase	3 (15.0%)	17 (85.0%)	20 (100.0%)	

Table 4 shows the relationship between RV, RV/TLC and FRC/TLC values with the mMRC scale. There is no significant correlations between mMRC scale and RV, RV/TLC and FRC/TLC values. RV/TLC values increased more on the mMRC scale ≥2 compared to the mMRC <2 scale of 70.6% or as many as 24 subjects. The value of FRC/TLC increased more on the mMRC scale ≥2 compared to the MmRC <2 scale of 85.0% or as many as 17 subjects.

Table 4. The Relationship Between RV, RV/TLC Values and FRC/TLC On The mMRC Scale In Stable COPD Patients

Category	MmRC		Total	*P*
	<2	≥2		
RV				
Normal	9 (27.3%)	24 (72.7%)	33 (100.0%)	0.351
Increase	1 (50.0%)	1 (50.0%)	2 (100.0%)	
RV/TLC				
Normal	0 (0.0%)	1 (100)	1 (100.0%)	0.385
Increase	10 (29.4%)	24 (70.6%)	34 (100.0%)	
FRC/TLC				
Normal	7 (46.7%)	8 (53.3%)	15 (100.0%)	0.085
Increase	3 (15.0%)	17 (85.0%)	20 (100.0%)	

Table 5 shows the relationship between RV, RV/TLC and FRC/TLC with a 6-minute walking test. There was no significant relationship between the 6-minute walking test scale and RV value. The value of RV/TLC when compared with the 6-minute walking test shows a significant correlation. The value of RV/TLC increased more in the 6-minute walking test

less than 350 meters. The relationship between the value of FRC/TLC with the 6-minute walking test showed a significant relationship but the FRC/TLC value increased more in the 6-minute <350 meters.

Table 5. The Relationship Between RV, RV/TLC and FRC/TLC Values on The 6-Minute Walking Test In Stable COPD Patients.?"

Category	6-minute walking test		Total	*P*
	<350	≥350		
RV				
Normal	24 (72.7%)	9 (27.3%)	33 (100.0%)	0.137
Increase	2 (100.0%)	0 (0.0%)	2 (100.0%)	
RV/TLC				
Normal	1 (100.0%)	0 (0.0%)	1 (100.0%)	0.004
Increase	25 (73.5%)	9 (26.5%)	34 (100.0%)	
FRC/TLC				
Normal	9 (60.0%)	6 (40.0%)	15 (100.0%)	0.003
Increase	17 (85.0%)	3 (15.0%)	20 (100.0%)	

Table 6 shows the relationship between RV, RV/TLC and FRC/TLC with exacerbations in 1 year. There was no significant relationship between exacerbations in 1 year and RV values. RV values that increased significantly were found in exacerbations in 1 year ≥2 compared to exacerbations in 1 year <2. The value of RV/TLC when compared to exacerbations in 1 year shows no significant relationship. The value of RV/TLC increased more in exacerbations in 1 year ≥2 compared to exacerbations in 1 year <2 by 64.7% or as many as 22 subjects. The relationship between the value of FRC/TLC and exacerbations in 1 year showed a significant relationship but the value of FRC/TLC increased more in exacerbations in 1 year ≥2 compared to exacerbations in 1 year <2 by 75.0% or as many as 15 subjects.

Table 6. Relationship Between RV, RV/TLC Values and FRC/TLC Against Exacerbations In 1 Year in Stable COPD Patients

Category	Exacerbation 1 years		Total	*P*
	<2	≥2		
RV				
Normal	13 (39.4%)	20 (60.6%)	33 (100.0%)	0.364
Increase	0 (0.0%)	2 (100.0%)	2 (100.0%)	
RV/TLC				
Normal	1 (100.0%)	0 (0.0%)	1 (100.0%)	0.404
Increase	12 (35.3%)	22 (64.7%)	34 (100.0%)	
FRC/TLC				
Normal	8 (53.3%)	7 (46.7%)	15 (100.0%)	0.009
Increase	5 (25.0%)	15 (75.0%)	20 (100.0%)	

DISCUSSION

A total of 35 study subjects (100.0%) were men. This is similar to the research from Ismail in the Persahabatan Hospital showing that most subjects are male (92.3%). Other studies from Travers et al and O'Donnell et al showed that most subjects are male (72.0% and 64.0% respectively).[7–9] In contrast to the study by Stroband et al in Leiden, there were fewer male gender categories (28.0%).[10]

Most of the study subjects' ages are over 60 years old (74.3%). The study from Ismail shows similar results, with 64,6% of subjects age 60-90 years old. Similar results were also reported by Travers et al mean age of the study subjects was 60 years, and in the study of O'Donnell et al, the mean age of the study subjects was 66 years.[8,9]

Subject nutritional status based on BMI in this study showed 42.9% of subjects with normal BMI, 22.9% with overnutrition, and 22.9% with obesity. Similar to Ismail's research, in the normal BMI category 61.5%. Results differ from Travers' study getting a BMI average of 26.8, which is also similar to O'Donnell et al's study getting an average BMI of 25.8, and research from Stroband et al.[8–10] with an average BMI of 26.2. The three studies that obtained obesity nutritional status had the highest average BMI.

In this case, the scale of tightness is the mMRC scale; in this study, the highest mMRC score is mMRC more than or equal to 2, as much as 71.4%, while the mMRC scale of less than 2 was 28.6%. This result is similar to Stroband et al's study in Leiden, which got the highest MmRC scale of more than 3.[10]

The value of the most 6-minute walking test in this study is a distance of 250–350 meters, as much as 54.3%, followed by a distance of more than 350 meters, as much as 25.7%, and a distance of 150–250 meters, as much as 20%. Similar to the study by Hartman et al getting a mean 6-minute road test in 91 COPD subjects of 319.2±97.5 meters, but different from the study of Balcells et al in Spain who received a midpoint test of the 6-minute road test on COPD subjects in the study, this is 440 meters.[11,12] This is also similar to the research by Nizet et al in the

Netherlands, who also got a mean test score of 6 minutes of 410 meters.[13]

The smoking history of the former smoker subject was 100.0%. Similar to the study of Balcells et al, the subjects who had and were smoking were 94.0% but different studies from Nizet et al, in their study of smoking with the subject smokers were 29.8%.[12,13] In this study, the severity of smoking is measured with the Brinkman Index. Most subjects were moderate smokers (57.0%), in contrast to Travers et al study and Stroband et al study which most subjects were heavy smokers.[8,10]

Symptoms in COPD subjects in this study were dominated by symptoms of 74.3% shortness of breath, while symptoms of chronic cough affected 25.7% of subjects. Slightly different from the study conducted by Kitaguchi et al, the most common clinical symptoms in subjects with COPD were symptoms of shortness of breath, which was 36.5%, while chronic cough was 28.2%.[14]

COPD patients in this study were mostly accompanied by 54.4% of comorbidities. In contrast to the research conducted by Nizet et al in the Netherlands, which obtained COPD subjects with comorbidities only 38.3% of whom had cardiovascular comorbidities 17%, diabetes mellitus 14.9%, hypertension 8.5%.[13]

There is no significant correlations between FEV_1 and RV, RV/TLC and FRC/TLC values. The residual volume is ≥120%, RV/TLC >30.0% and FRC/TLC >55.0% is smaller in degrees III-IV compared to degrees I-II. This is possible because the predicted RV values used are taken from European subjects. In contrast to the study of Dykstra et al in Rochester in 4774 subjects using a body plethysmograph and also predictive values used using predictions with the same race. There was a negative relationship between RV, RV/TLC and FRC/TLC with FEV_1 which means that the higher RV, RV/TLC and FRC/TLC in COPD patients the lower the FEV_1 value obtained. Weaknesses in the Dykstra et al study was that some patients did not remember the diagnosis of previous pulmonary disease that was told by their doctor.[6] In line with the study of Papaioannou et al in Greece 49 male subjects had a significant relationship (P<0.003) between an increase in the value of FRC/TLC with a decrease in FEV_1 value, the percentage of the relationship was 64%.[15]

The RV values increased more with symptoms of tightness, but there was no significant relationship with clinical symptoms. Similarly, the value of RV/TLC when compared with clinical symptoms showed a significant relationship, but the value of RV/TLC that increased in this study was more on the symptoms of shortness of breath compared to the symptoms of cough, (73.5%). In contrast to the study by Stroband et al, which examined 114 COPD patients who were divided into two groups, with and without chronic bronchitis, comparing the RV/TLC values showed that there were no significant differences (P=0.61) between events with chronic bronchitis and without chronic bronchitis, with 46.6% and 47.8%, respectively.[10]

The correlations between the value of FRC/TLC and clinical symptoms also showed a statistically significant relationship, but the value of FRC/TLC increased more in the symptoms of shortness of breath compared to the symptoms of chronic cough, which was 85.0%. In line with Parker et al's study in 20 patients with a prospective cohort method of five times observation, it was found that there was an increase in symptoms of shortness of breath compared to chronic cough associated with an increase in lung volume values in both RV, RV/TLC and FRC/TLC values. In the Parker et al study, there was an increase in trapped air and pulmonary hyperinflation, so symptoms of breathlessness were more dominant than chronic cough.[16]

This study obtained the result that there was no significant relationship between the mMRC scale and the RV value. This study found RV values increased in mMRC 2 by 50.0% (P=0.351). The higher the RV value, the higher the value of the mMRC obtained; this is because the RV prediction that is used to produce RV-predicted values does not use the value of Indonesian fiction. In contrast to the research from Gompertz et al in Germany conducted with a prospective cohort, they obtained a positive

relationship between the value of mMRC and the volume of residue, so that the higher the residual volume value, the higher the value of mMRC, with the relationship obtained at *P*=0.02.[17]

RV and TLC values increased more on the mMRC scale 2 compared to the mMRC <2 scale (70.6%). However, there is no significant correlation between RV/TLC and mmRC scale (*P*=0.385). In contrast to the study by Shin et al that divides the two groups, namely RV/TLC group ≥ 40.0% and RV/TLC value group <40.0% when linked to the mMRC scale, it is statistically significant so that the higher the RV/TLC value of a person, the more likely there will be pulmonary hyperinflation, and the higher the value of mMRC obtained.[18]

This study also tried to connect the value of FRC/TLC to the mMRC scale. This study found no significant relationship between FRC/TLC values that increased more on the mMRC scale 2 than the mMRC <2 scale of 17 subjects (85.0%). In contrast to the research by Parker et al showing a tendency to increase the mMRC scale with an increase in the value of FRC/TLC, with the increasing value of FRC/TLC in COPD patients, the mMRC scale also increased.[16] The tendency for an increase was also shown in the results of the study by Papaioannou et al, who obtained an increase in the value of FRC/TLC in the emphysema group, followed by an increase in the value of mMRC in the emphysema patient.[15]

This study found no significant relationship between the 6-minute walking test and RV value because of the limited subjects and the prediction used by Europeans. In addition, this study between FRC/TLC with a 6-minute walking test also showed a significant relationship, but FRC/TLC increased more in the 6-minute <350-meter walking test compared to the 6-minute >350-meter road test by 85.7%. In line with the Wijkstra et al study in 40 subjects, this study did not connect directly but obtained an increase in RV, FRC/TLC with a decrease of 6 minutes of walking test so that the RV value increased and FRC/TLC on COPD subjects decreased test values. Six-minute walking is obtained in COPD patients. This is explained by the occurrence of dynamic hyperinflation during activities.[19]

The value of RV/TLC when compared with the 6-minute walking test shows a significant correlation. The value of RV/TLC increased more in the 6-minute walking test less than 350 meters compared to the road test 6 minutes >350 meters at 74.3%. In line with research by Shin et al, which showed the difference between the value of RV/TLC more or less equal to 40% and less than 40% with a 6-minute walking test, this study found that there was a significant difference with decreased of 6MWT while hyperinflation occurred (*P*=0.045).[18]

There was no significant relationship between exacerbations in 1 year and RV values, but RV values did increase in subjects with lesser exacerbations. The relationship between the value of FRC and TLC and exacerbations in 1 year was also significant, but the value of FRC and TLC increased more in exacerbations by 75.0%. The study from Kim et al divided the COPD subjects with and without chronic bronchitis with 290 and 771 Subjects, respectively.[20] In this study, there is no significant relationship between lung volume and the number of exacerbations a year. The patient also underwent a thoracic CT examination to confirm existing abnormalities in the lungs. The results showed a significant relationship between RV values and FRC/TLC in the group without chronic bronchitis, and exacerbations were also statistically significant can see the tendency to increase lung volume with a 1-year exacerbation in the group without chronic bronchitis.

The value of RV and TLC when compared to exacerbations in a year shows a significant correlation. Subjects with exacerbations more than twice a year show an increase in RV and TLC by 64.7%. In line with the research of Shin et al which also looked at the relationship between RV and TLC values and the occurrence of exacerbations. Study by Shin et al also found a significant relationship between the value of RV and TLC and the occurrence of exacerbations. The more frequent exacerbations in COPD patients, the higher the RV/TLC value in those patients, with *P*=0.012.[18]

In contrast to research from Birmingham by Gompertz et al, conducted on 70 subjects with a retrospective cohort method, Gompertz et al looked at the relationship between exacerbations the prior year, three times or less with lung volumes such as RV and TLC.[17] There were no significant differences between exacerbations in the previous year (118.8% and 124.8%, respectively), but there was an increase in lung volume values in this case if the exacerbation was ≥3.

LIMITATION

This study has limitations in several ways, namely that it did not carry out an FRC examination using a body plethysmograph as a gold standard check and was most accurate in determining functional residual capacity. There was outnumbered female subjects in this study. This study also did not perform chest X-ray examinations, so it could not confirm spirometry results. Predictive values used for residual volume still use European predictions because Indonesia does not yet have a standard predicted residual volume value.

CONCLUSION

The mean value of RV in milliliters is 1490.61 (150-3470). The mean RV% prediction value is 64.11% (6-141). The mean RV/TLC value is 36.90% (6-57). The average value of FRC/TLC is 57.23% (37-79). There is no relationship between FEV_1 values and lung volume with clinical symptoms in stable COPD patients. There is no relationship between RV values, RV/TLC and FRC/TLC with FEV_1 values in stable COPD patients. There is no relationship between RV values with mMRC scale and the CAT scale. There is a significant relationship between the value of RV/TLC and the value of FRC/TLC with the mMRC scale, but only the value of FRC/TLC has a meaningful relationship with the CAT scale. There is no relationship between RV values and FRC/TLC with a 6-minute walking test and exacerbation within 1 year. There is a significant relationship between the value of RV/TLC with the 6-minute walking test. The higher the value of RV/TLC, the lower the value of the 6-minute walking test and the increase in exacerbation of 1 year in COPD patients. There is no relationship between RV values, RV/TLC and FRC/TLC with the Brinkman Index and COPD group.

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CONFLICT OF INTEREST

None.

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Original Article

The Correlations Between Clinical Characteristics and Inflammation Markers with Chest X-rays in COVID-19 Patients at Ulin Hospital

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Abstract

Background: Chest x-ray is one of the parameters used to estimate the severity and prognosis of COVID-19. Arterial oxygen saturation (SaO_2), partial pressure of arterial oxygen (PaO_2), and respiratory index (PaO/FiO_2) can also predict the disease severity. Other parameters, like inflammation markers, have also been used as predictors for prognosis. Based on those considerations, this study aimed to examine their connection and find their correlation.

Methods: This was an analytic observational retrospective study. The samples were moderate-critical COVID-19 patients in Ulin General Hospital Banjarmasin from July to December 2021 who met the inclusion and exclusion criteria. Statistical tests were used to see the relationship between clinical characteristics and inflammation markers with chest X-rays using various scoring systems (Brixia, sRALE, and modified Soetomo score).

Results: The total number of subjects was 67. The data analysis found that the severity of the disease had a significant relationship with the severity of the chest x-ray (P<0.001). The PF ratio also had a significant negative correlation (P<0.001) with the severity of the chest x-ray. For inflammation markers, NLR, CRP, and LDH significantly correlated with a chest x-ray. The patient's outcome was also associated with a chest X-ray (P<0.015).

Conclusion: There were significant correlations between clinical characteristics and inflammation markers on the chest X-ray severity, and sRALE was a better scoring system to assess chest X-ray severity than other scoring systems.

Keywords: COVID-19, chest X-ray, disease severity, inflammation markers, PF ratio

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INTRODUCTION

COVID-19 cases and deaths are still increasing every day. This situation requires a prediction system to identify the severity of COVID-19 and the risk of mortality.[1] Chest x-ray is one of the parameters used to estimate the severity and prognosis of COVID-19.[2] Arterial oxygen saturation (SaO_2), partial pressure of arterial oxygen (PaO_2), and respiratory index (PaO_2/FiO_2) can also predict the disease severity.[1]

Other parameters, like inflammation markers, have also been used as predictors for prognosis.[3] These variables complement each other. Based on those considerations, this study aimed to examine their connection and to find their correlation. Nevertheless, since chest X-rays have multiple scoring systems, we would like to compare them to see which correlates best with a clinical condition.

METHODS

This retrospective observational analytic study was performed at Ulin General Hospital. There were 245 samples of COVID-19 patients from July 2021 until December 2021, with disease severity ranging from moderate to critical.

These patients were diagnosed by reverse transcriptase-polymerase chain reaction (RT-PCR) testing and treated in an isolation ward. Patients with incomplete medical record data, lung disease(s), comorbidity that can disrupt the respiratory and blood profiles, or severe immunocompromised conditions were excluded. After that, there were only 67 samples that could be collected and analyzed.

From those samples, we collected data about chest X-rays, disease severity, blood gas analysis, and inflammation markers (NLR, ALC, LDH, and CRP) that were tested less than 48 hours after patients were admitted to the hospital. The chest x-rays of the patients will be assessed by two radiologists using three scoring systems already well known in COVID-19 (Brixia, sRALE, and modified Soetomo scoring system). The Brixia scoring system divides chest X-rays into six regions. Each region is assessed for infiltrates (0=normal/no infiltrate; 1=infiltrates in interstitial; 2=infiltrates in interstitial and alveolar, with most in interstitial; and 3=infiltrates in interstitial and alveolar, with most in alveolar). The total scores are 18.

The sRALE (simplified Radiographic Assessment of Lung Edema) scoring system divides chest X-rays into two regions. Each region is assessed for the percentages of consolidations and infiltrates in the lung (0 = no consolidation; 1 = <25% of consolidations; 2 = 25 to 50% of consolidations; 3 = 50 to 75% of consolidations; and 4 = >75% of consolidations). The total scores are 8. The modified Soetomo scoring system divides chest X-rays into six regions. Each region is assessed for the percentages of infiltrates (0=no infiltrate; 1=infiltrates <50%; and 2=infiltrates >50%). The total scores are 12.

Furthermore, for the latter, we also collected the outcome of the samples (survive or non-survive). The data were analyzed using univariate and bivariate correlations based on the result of the normality test using Kolmogorov-Smirnov.

RESULTS

As we can see from Table 1, the majority of the samples were male (61.2%), aged <65 years old (74.6%), in critical condition (49.2%), had two comorbidities (29.8%) and survived (73.1%). Moreover, from the inflammation markers in Table 1, there were increased NLR (80.6%), decreased ALC (77.6%), increased CRP (100%), and increased LDH (97.0%). In blood gas analysis, it was observed that the PF Ratio ranged from >100 to 200 and had the highest frequency (35.8%).

Table 1. Demographic Characteristics and Inflammation Markers of Patients

Variables	N	%
Demographic Characteristics		
Gender		
Male	41	61.2
Female	26	38.8
Age (mean±SD)		
<65 years (49.83±11.218)	50	74.6
≥65 years (71.29±5.610)	17	25.4
Disease Severity		
Moderate	14	20.9
Severe	20	29.9
Critical	33	49.2
Comorbidities		
No comorbidity	11	16.4
1 Comorbidity	19	28.4
2 Comorbidities	20	29.8
≥3 Comorbidities	17	25.4
Outcome		
Survive	49	73.1
Non-survive	18	26.9
Inflammation Markers		
NLR (mean±SD)		
<3.13 (2.28±0.616)	13	19.4
≥3.13 (7.62±4.089)	54	80.6
ALC (mean±SD)		
>1500 (1772.56±263.570)	15	22.4
≤1500 (911.63±290.984)	52	77.6
CRP (mg/dl) (mean±SD)		
<6	0	0.0
≥6 (106.13±67.500)	67	100
LDH (U/L) (mean±SD)		
≤220 (186.5±27.577)	2	3.0
>220 (980.8±564.739)	65	97.0
PF Ratio (mean±SD)		
>300 (383.54±49.345)	16	23.9
>200–300 (240.39±29.613)	13	19.4
>100–200 (143.8±25.470)	24	35.8
≤100 (81.13±14.037)	14	20.9

Table 2. Correlation between disease severity and chest x-ray.

Variable	Total	Score Mean±SD	*P* (r)
Disease Severity (Brixia)			
Moderate	14	4.29±2.301	**<0.001*** (0.475)
Severe	20	7.20±2.802	
Critical	33	8.55±3.241	
Disease Severity (sRALE)			
Moderate	14	2.64±0.929	**<0.001*** (0.466)
Severe	20	3.85±1.137	
Critical	33	4.36±1.141	
Disease Severity (Soetomo)			
Moderate	14	3.93±1.592	**<0.001*** (0.406)
Severe	20	5.85±1.927	
Critical	33	6.39±1.749	

Note: **Spearman's rho*

Table 3. Correlation between blood gas analysis (PF ratio) and chest X-ray

PF Ratio	Total	Brixia Mean±SD	*P* (r)	sRALE Mean±SD	*P* (r)	Soetomo Mean±SD	*P* (r)
>300	16	5.31±3.301		2.94±1.181		4.56±2.190	
>200–300	13	5.92±2.813	**<0.001***	3.38±1.121	**<0.001***	4.92±1.801	**<0.001***
>100–200	24	8.29±1.801	(-0.452)	4.08±0.929	(-0.538)	6.21±1.250	(-0.436)
≤100	14	8.93±3.452		4.93±1.141		6.93±2.129	

Note: **Spearman's rho*

Table 4. Correlation between inflammation markers and chest X-ray

Variable	Total	Brixia Mean±SD	*P* (r)	sRALE Mean±SD	*P* (r)	Soetomo Mean±SD	*P* (r)
NLR							
<3.13	13	5.85±3.387	0.152	3.15±1.344	**0.014***	4.92±2.253	0.122
≥3.13	54	7.59±3.259	(0.177)	4.02±1.205	(0.298)	5.91±1.896	(0.191)
ALC							
>1500	15	7.87±4.033	0.815	3.73±1.624	0.349	6.13±2.356	0.824
≤1500	52	7.07±3.124	(-0.029)	3.88±1.166	(-0.116)	5.59±1.881	(-0.028)
CRP (mg/dl)							
<6	0	-	**0.004***	-	**0.002***	-	**0.002***
≥6	67	7.25±3,332	(0.346)	3.85±1.270	(0.374)	5.72±1.991	(0.371)
LDH (U/L)							
≤220	2	5.00±1.414	**0.04***	4.00±0.000	**0.049***	5.00±1.414	0.075
>220	65	7.32±3.354	(0.251)	3.85±1.289	(0.241)	5.74±1.289	(0.219)

Note: **Spearman's rho*

In Table 2, we obtained that disease severity had a significant correlation with all chest x-ray scoring systems (*P*<0.001). The correlation coefficient (r) showed a good relationship, with the highest correlation belonging to the Brixia (r=0.475). From blood gas analysis, we also found that the PF ratio had a significant negative correlation with all chest x-ray scoring systems (Table 3). Nevertheless, in this case, sRALE had the highest correlation with the PF ratio (r = -0.538).

From Table 4, we can see significant correlations between some inflammation markers and chest X-rays. CRP and LDH significantly correlated with the severity of the chest x-ray. CRP correlated with all chest x-ray scoring systems, and sRALE had the highest correlation (r=0.374). Meanwhile, LDH had correlations with two scoring systems (Brixia and sRALE), with Brixia (r=0.251) having a slightly better correlation than sRALE (r=0.241). The NLR only correlated with sRALE. Meanwhile, ALC did not correlate with chest x-rays.

There was also a correlation between outcome and chest x-ray (based on Table 5), but only if we used the sRALE scoring system (*P*<0.015), while other scoring systems did not correlate at all.

Table 5. Correlation between outcome and chest X-ray

Variable	Total	Score Mean±SD	*P*
Outcome (Brixia)			
Survive	49	7.10±3.601	0.355
Non-survive	18	7.67±2.497	
Outcome (sRALE)			
Survive	49	3.65±1.316	**0.015***
Non-survive	18	4.39±0.979	
Outcome (Soetomo)			
Survive	49	5.55±2.102	0.219
Non-survive	18	6.17±1.618	

Note: **Mann-Whitney U*

DISCUSSION

In this study, we gathered 67 samples from patients. Most of them were male (61.2%). It has the same result as existing studies, such as Mukherjee et al and Abate et al.[4,5] This might be caused by several things, such as higher and more active ACE2 expression in males than females. The expression of transmembrane protease serine 2 (TMPRSS2), which is affected by androgen receptors in males, also enhances the effect of the SARS-CoV-2 spike protein, so the virus can enter the body more easily. Another thing that makes males more susceptible to COVID-19 is that females have a better immune response (influenced by estrogen) and higher nitric oxide levels (NO).[4]

Another piece of data that we obtained from Table 1 was age. About 74.6% of subjects were under 65 years old. Karyono et al said that productive age patients are more affected by COVID-19 because, in that age range, patients are still actively working and dealing with many people in their daily activities, so they are more easily exposed to COVID-19.[6] In terms of disease severity, this study found that 49.2% of the sample had critical conditions. Because the population for this study was taken from July 2021 to December 2021, the Delta variant of COVID-19 was dominantly hitting Indonesia during this period. This variant has more severe cases and a higher risk of being admitted to the intensive care unit than the previous variant. [7–9]

However, this study found that the number of living patients was greater than that of those who died. Various things can cause this. First, the administration of vaccines has already started. Second, many patients who died in this study population could not be used as research samples because they did not have complete medical records, so they were excluded.[8,10]

Another exciting thing that we obtained was that the number of comorbidities did not determine the prevalence. Singh et al published the same thing.[11] However, in the study of Haryati et al, it was stated that the number of comorbidities affected the mortality in COVID-19 patients.[3] Another study by Haryati et al also pointed out that the inflammation process caused changes in inflammatory marker values due to COVID-19 and released various types of inflammatory mediators during cytokine storms.[12]

In blood gas analysis, we observed a decrease in PF ratio with more samples, most of which were in the range >100 to 200. It has a similar result to a study by Tang et al, where COVID-19 decreased the PF ratio by an average of 198.5.[13] The reason why there was a decreased PF ratio was due to intrapulmonary shunt that happened because of damaged alveoli from viral infections.[14]

Table 3 shows that the disease severity of COVID-19 correlates with chest x-ray severity, no matter which scoring is used to assess the severity of chest X-rays (P<0.001). However, Brixia had the strongest correlation with r=0.475, followed by sRALE with r=0.466, and the modified Soetomo score with r=0.406. This result is the same as a study from Setiawati et al in Soetomo Hospital.[15]

Duc et al also did a similar study but stated that sRALE has the strongest correlation, not Brixia.[16] Toussie et al studied the correlation between the number of infiltrates found in chest X-rays and the severity of the disease and also discovered a correlation.[17] Chen et al said that when there were mild respiratory symptoms, they were usually followed by ground glass opacity (GGO) in a chest x-ray. Then, after the virus started to replicate faster, it would attack bronchioles and alveolar epithelia, causing leakage in the alveolar cavity. This will make conditions called “white lung” and their symptoms worse.[18]

For the blood gas analysis, there was a negative correlation between the PF ratio and chest x-ray (P=0.001), with sRALE having the highest correlation coefficient with r = -0.538. Baratella et al and Velissaris et al did similar studies, although they used different systems to assess the chest X-ray severity. They discovered a correlation between chest X-rays and PF ratio.[19,20] This happened because there were infections in the epithelia of the lung parenchyma, and this condition disrupted gas exchanges.[19]

However, in some cases, the PF ratio did not correlate with chest X-rays because the hypoxemia condition was not only affected by the lung parenchymal but also by its vascularity.[21] This theory is also supported by Kumar et al. They stated that sometimes the patient had respiratory failure type 1, but his chest X-rays still looked normal because the chest X-rays were unable to detect thromboembolism.[22]

Inflammation markers also correlated with chest X-rays, although not all of them. CRP correlated with all chest X-ray scoring systems. LDH correlated with two scoring systems (sRALE & Brixia), while NLR correlated only with sRALE. However, ALC did not correlate at all with chest X-rays. Sensusiati et al also observed the same thing with ALC.[23] However, Wagner et al said that ALC

could be used to measure the disease severity of COVID-19.[24] Fachri et al reported a correlation between comorbidities and chest X-rays with CRP.[25]

Geetika et al also studied the correlation between chest X-rays (using Brixia and sRALE) and laboratory parameters such as CRP, ferritin, LDH, D-dimer, and leukocyte. In that study, there was a correlation between chest x-ray and laboratory parameters.[26] There is also another study that discovered a correlation between chest X-rays with CRP and LDH.[27] CRP and LDH are inflammatory markers that indicate inflammations and damage in cells. In this case, the CRP and LDH values indicate the amount of alveolar damage due to viral infection, which is reflected in the chest x-ray.[28,29]

Zhang et al were the first team to find a correlation between NLR and lung lesions, however, they were using a CT scan.[30] Garg et al also had a similar result to our study, where they obtained a correlation between NLR, chest X-rays and outcome.[31] A study from Kotok et al also reported a correlation between NLR and chest X-rays (using sRALE).[32] NLR can affect the chest x-ray because, in COVID-19, neutrophils will increase and extravasate to the alveoli, leading to neutrophilic mucositis and thus creating infiltrates in the chest x-ray. In addition, lymphocyte cells will experience destruction due to infection, causing a decrease in the number of lymphocytes and increasing the NLR value.[33]

This study found a correlation between patient outcomes and chest X-rays using sRALE scoring. Meanwhile, when using other scoring systems, there were no correlations. The correlation between patient outcomes and chest X-rays has been extensively studied. However, there are still a few studies that tried to compare various scorings. Borghesi et al discovered no correlation between the chest X-ray severity (using the Brixia score) and the outcome. Chest X-rays are only meaningful for the outcome if at least one other predictor factor is added as a variable.[34] This research was later refuted by Balbi et al, who reported a positive correlation (without considering comorbidities) between the Brixia score and the risk of death.[35]

Yasin et al also found that the severity score (using sRALE) positively correlated with disease severity and death.[36] Kodikara et al also tried to examine the sRALE scoring system for risk of death. This study also attempted to make two modified scores from sRALE. The first score was a combination of the sRALE and RALE system assessments, while the second was a combination of the sRALE system and Brixia. The final results of this study indeed obtained a positive correlation between the severity of chest X-rays and mortality, and the second modified system (combined sRALE and Brixia) had the best correlation rate.[37]

Kotok et al also reported that the group of patients with RALE scores with a median of 3 had more hospital admissions compared to those with a median of 2, and those with RALE scores with a median of 7 were more at risk for ICU admission.[38] However, some studies stated that there was no significant relationship between outcomes and chest X-rays because it relied on comorbidities.[39]

LIMITATION

There are several limitations to this study. First, it was a single-center study with a relatively small sample. Second, since this study only focused on the total scores of the scoring systems, it lacked a correlation between the regions of chest X-rays and clinical conditions. And lastly, it was short of a correlation between the score and comorbidities.

CONCLUSION

There is a correlation between clinical characteristics (disease severity, blood gas analysis, and outcome) and inflammation markers (NLR, CRP, and LDH) with chest x-ray severity. In this study, we also found that sRALE is a better scoring system to measure chest x-ray severity than other scoring systems because it correlates the most with other variables. sRALE is shown to be a better scoring system because it is simple while still emphasizing the severity of lung conditions. The Brixia only measures the presence of the infiltrate but tends to ignore the size of it. The modified Soetomo score

tries to combine the scoring system of sRALE and Brixia, but it still lacks the simplicity of sRALE.

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CONFLICT OF INTEREST

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Original Article

The Effect of Inhaled Ipratropium Bromide as a Premedication For Bronchoscopy on Dyspnea, Cough, and Tracheobronchial Secretion

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Abstract

Background: Bronchoscopy is a minimally invasive procedure used for diagnostic examination and intervention of the airways. Patient comfort and cooperation during bronchoscopy are very important because they affect the success and outcome. The sympathetic anticholinergic effect of ipratropium bromide can improve procedure tolerance and airway visualization. This study was conducted to analyze the effect of inhaled ipratropium bromide as a bronchoscopy premedication for the assessment of dyspnea, cough, and tracheobronchial secretion.

Methods: This was a clinical study with a quasi-experimental pretest-posttest control group design in pulmonary patients who underwent bronchoscopy at Dr. Moewardi General Hospital Surakarta in October 2021 using consecutive sampling. The subjects of the study were divided into an intervention group with inhaled ipratropium bromide and a control group without inhaled ipratropium bromide. The Borg scale of dyspnea and the visual analog scale (VAS) score of cough were assessed before and after bronchoscopy in both groups. The grading of tracheobronchial secretion was assessed during bronchoscopy.

Results: Thirty-six pulmonary patients who underwent bronchoscopy were included in this study. The intervention group showed a lower Borg scale (0.28±0.57) and VAS score (3.22±8.54), lower tracheobronchial secretion grading, and there was a significant difference compared to the control ($P \leq 0.05$).

Conclusion: There was a significant difference in the Borg scale of dyspnea, VAS score of cough, and the grading of tracheobronchial secretion in patients undergoing bronchoscopy as an effect of ipratropium bromide inhalation.

Keywords: Borg scale of dyspnea, bronchoscopy, grading of tracheobronchial secretion, inhaled ipratropium bromide, VAS score of cough

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INTRODUCTION

Bronchoscopy is a minimally invasive procedure used for diagnostic and interventional examination of the airways. Bronchoscopy is generally performed using light sedation and intravenous (IV) premedication. Bronchoscopy can be performed without sedation or under general anesthesia if needed.[1,2] The invasive procedure of bronchoscopy causes discomfort for the patient. Complications of bronchoscopy include anxiety, dyspnea, coughing, and pain. Complications of bronchoscopy increase patient discomfort.[1–3]

Patient comfort and cooperation during bronchoscopy are very important because they affect the success and outcome. A good doctor-patient relationship, informed consent, and the use of premedication are expected to reduce anxiety and minimize complications experienced by patients.[2] In 2011, the American College of Chest Physicians stated that optimal procedure conditions are achieved when the patient is comfortable, the doctor can perform the procedure, and the risk is minimal.[4]

Premedication with anticholinergics during bronchoscopy procedures is used to reduce excessive secretion caused by general anesthetics. Anticholinergic drugs are still being used as premedication in health centers.[1,4] The main rationale for using anticholinergic agents during bronchoscopy is to improve visualization of the tracheobronchial tree by their antisecretory effect, prevent the bronchoconstriction reflex, and prevent vasovagal phenomena.[4] Anticholinergic drugs such as atropine, glycopyrrolate, and ipratropium bromide are used in bronchoscopy because of their sympathetic effect in

preventing vasovagal reactions such as bradycardia, coughing, and airway secretion. Anticholinergic sympathetic effects may increase procedure tolerance and airway visualization.[4,5]

Premedication with atropine has been commonly used in bronchoscopy procedures. Ipratropium bromide is an anticholinergic agent with a low systemic effect. Ipratropium bromide is a synthetic quaternary ammonium congener of atropine with atropine bronchodilator properties but minimal systemic absorption.[1,5]

Dyspnea can be assessed using the Borg scale, baseline dyspnea index (BDI), or transition dyspnea index (TDI). The Borg scale was modified from its original form to a 10-point scale with verbal expressions of severity associated with a specific number.[6,7] The modified Borg scale has good reproducibility in healthy individuals and can be applied to patients with cardiopulmonary disease as well as to statistical parameters.[7]

Cough control is very important for quality bronchoscopy because it makes visualization of the bronchi easier and helps obtain good samples. Cough severity can be assessed with subjective or objective tools.[8,9] A subjective evaluation of cough severity was assessed by a questionnaire. Methods that can be used to assess cough are the visual analog scale (VAS), cough symptoms score (CSS), simplified cough score (SCS), and cough severity diary (CSD).[8–12]

Hypersecretion of airway mucus makes visualization difficult during bronchoscopy. Williams et al assessed tracheobronchial secretion using a scale of 1 to 3 based on the presence or absence of the tracheobronchial secretion and the amount of saline solution used for washing. Reduced tracheobronchial secretion will facilitate bronchoscopy procedures and increase patient comfort.[13,14]

Ipratropium bromide works by blocking the muscarinic (M) receptors. Muscarinic antagonists reduce mucus secretion, increase the ability of the lungs to clear airway secretion, and reduce airway constriction due to activation of the parasympathetic nervous system.[4,5] Ipratropium bromide can also reduce dyspnea and coughing. The therapeutic effect of ipratropium bromide is in the form of an anticholinergic effect that inhibits the vagal reflex through an acetylcholine antagonist mechanism.[1,5] This study aims to determine the effect of inhaled ipratropium bromide as a bronchoscopy premedication for the assessment of dyspnea, cough, and tracheobronchial secretion. The results of this study are expected to strengthen the comfort level of the bronchoscopy procedure and increase the knowledge base in the fields of pulmonology and respiratory medicine.

METHODS

The study had a quasi-experimental pretest and posttest control group design for the assessment of dyspnea and cough. Posttest-only control group design for assessment of tracheobronchial secretion. The study population consisted of patients who underwent bronchoscopy procedure at the Dr. Moewardi General Hospital Surakarta in October 2021. The sampling technique was consecutive sampling. This study involved 36 patients. The subjects were grouped into the intervention and control groups.

The subjects were assessed for dyspnea with a modified Borg scale and cough with the VAS before bronchoscopy premedication. The intervention group was given inhaled ipratropium bromide (4 ml/1 mg) as a premedication for bronchoscopy. An inhaled solution of ipratropium bromide (4 ml) is given by nebulizer 20-40 minutes before bronchoscopy. The control group underwent standard bronchoscopy preparation. The assessment of tracheobronchial secretion grading is done during bronchoscopy. A second assessment of dyspnea and cough was performed after the bronchoscopy was completed.

The inclusion criteria for the study were pulmonary patients who were to undergo a bronchoscopy procedure at Dr. Moewardi General Hospital Surakarta, patients with lung tumors, mediastinal tumors, minimal pleural effusions, pneumothorax, age ≥18 years, and patients who could read and write. The exclusion criteria were

patients with allergies to ipratropium bromide, impaired consciousness, hemodynamic instability, cardiovascular disorders, hearing loss, cognitive or psychiatric disorders, asthma, and chronic obstructive pulmonary disease (COPD).

The study has been approved by the Ethics Committee of the Dr. Moewardi General Hospital Surakarta/Faculty of Medicine, Universitas Sebelas Maret Surakarta. Data analysis was carried out using SPSS version 19 for Windows, and data presentation was done using Microsoft Office 2010. All study data were tested for normality using the Shapiro-Wilk normality test because the sample size was <50 subjects. A value of *P*>0.05 means the subject in the study is homogeneous.

This study used a paired t-test for paired samples (pretest and posttest) and an independent t-test in the sample and intervention groups if the scale of numerical data and data distribution were normal. The study data was tested by the Mann-Whitney test to determine if the numerical scale of the data distribution was not normal. The Wilcoxon test was carried out if the two groups were paired and the data distribution was not normal. The unpaired group categorical data scale was tested using the Chi-Square test or Fisher's Exact test. The limit of significance is a value of *P*=0.05, which means it is statistically significant.

RESULTS

The demographic characteristics of the patients are presented in Table 1. The two groups of patients did not differ significantly in terms of age, sex, history of smoking, lung disease, or interventional procedures.

The modified Borg scale pretest in the intervention group had a mean value of 1.56±1.20. The mean of the modified Borg scale posttest increased to 1.83±1.42. The increase in the Borg scale was not statistically significant (*P*=0.059). The mean of the Borg scale at the pretest in the control group was 1.28±1.36. The mean Borg scale at the posttest in the control group increased to 2.44±1.95. The increase in the Borg scale was statistically significant, with *P*=0.004.

The changes between the two groups showed that in the intervention group patients, there was a mean increase of 0.28±0.57, and in the control group patients, it was 1.17±1.15. The difference in changes in the modified Borg scale (pretest-posttest) between the intervention and control groups was statistically significant, with *P*=0.014. The difference in the modified Borg scale between the treatment group and the control group can be seen in Table 2.

Table 1. Basic characteristics of research subjects.

Characteristic	Groups		*P*
	Intervention (n=18)	Control (n=18)	
Age	61.61±7.11	55.89±12.17	0.096
Sex			
Male	14 (77.8%)	11 (61.1%)	0.278
Female	4 (22.2%)	7 (38.9%)	
History of smoking			
Positive	13 (72.2%)	8 (44.4%)	0.091
Negative	5 (27.8%)	10 (55.6%)	
Lung disease			
Pleural effusions	4 (22.2%)	2 (11.1%)	0.553
Pneumothorax	2 (11.1%)	3 (16.7%)	
Mediastinal tumors	4 (22.2%)	3 (16.7%)	
Lung tumors	8 (44.4%)	10 (55.6%)	
Interventional procedure			
Bronchial wash	11 (61.1%)	16 (88.9%)	0.101
Forceps biopsy and bronchial wash	3 (16.7%)	0 (0.0%)	
Bronchial brush dan bronchial wash	4 (22.2%)	2 (11.1%)	

Table 2. Differences in the modified Borg scale between the treatment group and the control group.

Groups	Pretest	Posttest	*P*	Difference
Intervention	1.56±1.20	1.83±1.42	0.059	0.28±0.57
Control	1.28±1.36	2.44±1.95	0.004	1.17±1.15
P	0.612	0.211	---	0.014

The mean VAS scores on the pretest in the intervention group were 12.61±13.26. The mean VAS scores on the post-test in the intervention group rose to 15.83±11.37. The increase in the VAS scores was not statistically significant (*P*=0.114). The mean VAS score on the pretest in the control group using standard bronchoscopy preparation was 15.33±16.66. The mean posttest VAS scores in the control group increased to 32.56±25.40. The increase in the VAS score was statistically significant, with *P*=0.001.

Table 3. Differences in the cough VAS scores between the intervention group and the control group.

Groups	Pretest	Posttest	*P*	Difference
Intervention	12.61±13.26	15.83±11.37	0.114	3.22±8.54
Control	15.33±16.66	32.56±25.40	0.001	17.22±17.32
P	0.742	0.015	---	0.009

The change between the two groups showed that the intervention group had a mean increase of 3.22±8.54 and the control group had 17.22±17.32. The difference in the change VAS scores (pretest-posttest) between the intervention and the control group was statistically significant with *P*=0.009. The difference in VAS scores between the intervention group and the control group can be seen in Table 3.

Table 4. Differences in the grading of tracheobronchial secretion between the treatment group and the control group.

Variable	Groups		*P*-value
	Intervention (n=18)	Control (n=18)	
Tracheobronchial Secretion Grading	12 (66.7%)	4 (22.2%)	0.012
Grade 1	5 (27.8%)	12 (66.7%)	
Grade 2	1 (5.6%)	2 (11.1%)	
Grade 3	12 (66.7%)	4 (22.2%)	

Assessment of tracheobronchial secretion was performed at the time of bronchoscopy. The grading of tracheobronchial secretion in the intervention group mostly tended to be grade 1, which was 12 patients (66.7%), while in the control group, it tended to be grade 2, which was 12 patients (66.7%). The difference in tracheobronchial secretion grading between the intervention and control groups was statistically significant with *P*=0.012. The difference in the grading of tracheobronchial secretion between the intervention and control groups can be seen in Table 4.

DISCUSSION

The number of male subjects in this study was 25 patients (69.44%). The American Cancer Society stated that patients with lung cancer in the United States in 2021 would be around 235,760 new cases of lung cancer (119,100 in men and 116,660 in women) and about 131,880 deaths from lung cancer (69,410 in men and 62,470 in women).[15,16] Lung cancer is the most common type of cancer in men in Indonesia, and the fifth most common of all types of cancer in women.[16,17]

The results of hospital-based research from 100 hospitals in Jakarta in 2017 showed that lung cancer was the most common case in men and the fourth most common in women, and was the leading cause of death in both men and women.[16] Data from the Global Burden of Cancer Study (Globocan) 2020 stated that the number of new cases of lung cancer patients in Indonesia in 2020 was 25,943 (14.1%) in men.[17]

The dominant risk factor for lung cancer is a history of smoking.[16,18] The group of patients with a high risk of developing lung cancer includes patients aged >40 years with a history of smoking ≥30 years and smoking cessation within ≥15 years before the examination, or patients ≥50 years with a history of smoking ≥20 years and the presence of at least one other risk factor. This study showed that 21 patients (58.3%) were smokers.[16]

The most common lung disease in this study was lung tumor. Lung tumor was experienced by 18 patients (50%). Patients who present with lung tumors will undergo diagnostic procedures. Bronchoscopy is the main procedure for diagnosing lung cancer. This procedure can be used to obtain tissue or specimens for cytologic and histopathological examination.[19] Setiadi et al reported that the most frequent indication for bronchoscopy

performed in the Dr. Moewardi General Hospital Surakarta was a lung tumor (45.66%).[20]

Dyspnea is one of the dependent variables assessed in this study. Dyspnea was assessed with a modified Borg scale. Based on the results of this study, it could be seen that the administration of inhaled ipratropium bromide before bronchoscopy was able to prevent an increase in dyspnea after bronchoscopy. Bronchoscopy is a minimally invasive procedure that can cause psychological stress or anxiety. Yildirim et al discovered that anxiety before bronchoscopy and the length of the bronchoscopy procedure were related to the level of patient discomfort.[3]

Psychological stress triggers the hypothalamus to activate the autonomic system (sympathetic and parasympathetic). Activated parasympathetic nerves cause the release of acetylcholine. Acetylcholine will bind to M3 receptors on bronchial smooth muscle. The binding of acetylcholine and M3 receptors will result in an increase in respiratory rate and bronchospasm, which can cause dyspnea.[1,3,21]

A study related to the effect of ipratropium bromide as premedication on the assessment of dyspnea has never been performed before. The study of inhaled ipratropium bromide's effect as a bronchoscopy premedication was conducted by Inoue et al. Inoue et al reported that ipratropium bromide significantly prevented a decrease in forced expiratory volume (FEV) and peak flow rates (PFR).[22]

Based on the results of this study, the administration of inhaled ipratropium bromide before bronchoscopy could prevent increased coughing after bronchoscopy. Yildirim et al stated that discomfort and cough were the main effects of bronchoscopy.[3] Bronchoscopy can cause mechanical and chemical stimuli that result in irritation of the cough receptors. Cough stimulation continues to efferent nerve fibers in the vagus nerve, trigeminal nerve, glossopharyngeal nerve, and phrenic nerve. Cough stimuli will be transmitted to the cough center in the medulla and then to the efferent nerve fibers, stimulating cough to the effector. The cough reflex occurs in the effectors.[23]

Administration of ipratropium bromide inhibits cholinergic transmission of cough impulses. Ipratropium bromide reduces the excitability of cough receptors so that cough impulses are transmitted to the cough center. The binding of acetylcholine and M3 receptors due to vagus nerve stimulation is inhibited by ipratropium bromide. Inhibition of acetylcholine binding and M3 receptors can reduce tracheobronchial secretion, which also affects cough control.[21]

This study has different results from the previous study. Rubins et al pointed out that the use of ipratropium bromide as a premedication in elderly patients during bronchoscopy did not produce clinical benefits such as coughing, wheezing, changes in pulse rate, blood pressure, or oxygen saturation. Rubins et al used inhalation of normal saline solution in the placebo group. Inhaling normal saline can induce mucus secretion. Excessive mucus secretion results in coughing.[24]

The grading of tracheobronchial secretion is as follows: grade 1 if there is almost no secretion; grade 2 if normal saline is required for rinsing; and grade 3 if the secretion is excessive and difficult to see even after rinsing. One aliquot contains 5 ml of normal saline solution. A statistical test proved that the grade of tracheobronchial secretion in the intervention group was lower than in the control group.

The result of tracheobronchial secretion grading in this study was similar to the study of Wang et al. The study of Wang et al proved that the inhalation of ipratropium bromide before the bronchoscopy procedure indicated a practical benefit on airway secretion (P=0.02).[14] Cowl et al had different results regarding the use of anticholinergics in bronchoscopy procedures. Cowl et al reported that tracheobronchial secretion was not statistically different in patients treated with anticholinergic drugs when compared with the placebo group. Cowl et al used atropine injection as a bronchoscopy premedication agent.[25]

The bronchoscopy procedure increases tracheobronchial secretion. Ipratropium bromide blocks cholinergic receptors and decreases the production of cyclic guanosine monophosphate

(cGMP). A decline in cGMP will decrease contraction of the smooth muscles. Ipratropium bromide dilates bronchial smooth muscle and inhibits salivary and mucous gland secretions. Inhalation of ipratropium bromide is a more potent antimuscarinic and smooth muscle bronchodilator than atropine.[14,26]

LIMITATION

The research subjects included in the study were patients with lung tumors and mediastinal tumors. The criteria for tumor size and location have not been explained in detail so all patients with lung tumors and mediastinal tumors can be included in this study. The large size of the tumor and pressing on the bronchi will cause more complaints of dyspnea, thus affecting the assessment of dyspnea. The research subjects' responses to the Borg scale for dyspnea and VAS score for cough were influenced by subjectivity and the subject's ability to understand the researcher's explanation.

CONCLUSION

Administration of inhaled ipratropium bromide affects the difference in the Borg scale of dyspnea, the VAS score of cough, and the grading of tracheobronchial secretion in patients undergoing bronchoscopy procedures.

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CONFLICT OF INTEREST

None.

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REFFERENCE

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Original Article

Analysis of Volatile Organic Compounds in the Exhaled Breath of COVID-19 Patients

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Abstract

Background: It has been more than 2 years since COVID-19's first cases were reported in 2019. Rapid diagnosis of COVID-19 is necessary to prevent its spread. A sample for COVID-19 testing is collected by a naso-oro-pharyngeal swab. This procedure is often uncomfortable and requires a trained examiner. Exhaled breath contains thousands of volatile organic compounds (VOC), which are likely to change during infection. This study aimed to analyze the difference in VOC in the exhaled breath between COVID-19 and healthy subjects.

Methods: A cross-sectional study was carried out, recruiting 90 confirmed cases of COVID-19 and 42 healthy subjects. A sample of exhaled breath was collected by using a 500-mL airbag in both groups. The sample was analyzed using an arrayed sensor breath analyzer to quantify the concentration of CO_2, C_7H_8, C_6H_{14}, CH_2O, NH_4, TVOC, NO_2, PM1.0, CO, NH_3 and Acetone.

Results: The medians of CO_2, NH_4, TVOC, NO_2, and acetone were significantly lower in COVID-19 patients compared to healthy subjects (respectively 607.3 vs 1175.1; 0.0 vs 1.05; 0.05 vs 146.6; 0.04 vs 1.55; 0.0 vs 0.23) while C_7H_8, CH_2O, CO, and NH_3 were significantly higher (respectively 0.92 vs 0.0; 0.55 vs 0.01; 0.24 vs 0.0; 1.99 vs 0.67; all with $P<0.05$.). Furthermore, we found that NH_4, acetone, NH_3, and CO were positively correlated with the severity of COVID-19, while CO_2 and TVOC were negatively correlated.

Conclusion: COVID-19 patients emit distinctive VOC profiles in comparison with healthy subjects, and this is related to the severity of the disease.

Keywords: COVID-19, diagnosis of COVID-19, volatile organic compounds

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INTRODUCTION

Back on December 31, 2019, the World Health Organization (WHO) China Country Office reported several cases of pneumonia with unknown causes, later identified as Coronavirus disease 2019 (COVID-19) cases.[1] COVID-19 is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2). This virus is the third in the Corona family that causes epidemic and continually becomes pandemic.[2] Until now, it has already infected more than 600 million people in the world and caused more than 6 million deaths.[3]

Rapid diagnosis is one of the key means of controlling the pandemic situation. Standard confirmation of acute SARS-CoV-2 infection is based on the detection of unique viral sequences by nucleic acid amplification tests (NAATs), such as reverse-transcription polymerase chain reaction (RT-PCR).[4] The procedure is not widely available, requires a long processing time, and is expensive in many countries. Therefore, developing a test that is inexpensive yet rapid and reliable to diagnose COVID-19 is needed. The rapid diagnostic test or RDT, which is an antigen-detection diagnostic test designed to directly detect SARS-CoV-2 proteins, was widely developed.[5]

Both of the procedures involve testing the sample obtained through respiratory specimens. Testing combined nasopharyngeal and oropharyngeal swabs from one individual has been shown to increase sensitivity and improve reliability.[4] Although obtaining the sample is generally considered safe, it requires semi-skilled staff and is

often uncomfortable, and several complications have been reported, with the possibility of more incidents escaping systemic recording. Several complications of pharyngeal swabs include a break of the swab's tip, foreign body sensation, epistaxis, dislocation of the temporomandibular joint, and leakage of the cerebrospinal fluid.[6] Although only a small number of complications are reported, raising awareness is needed. Moreover, inventing a new testing procedure with fewer complications while remaining reliable is a better alternative.

Volatile organic compounds (VOCs) are organic compounds that evaporate easily at room temperature. VOCs can be derived from the environment (exogenous), taken through inhalation or ingestion, or produced within the body.[7] Recent studies have shown at least 1765 VOCs can be detected in humans. Physiological metabolism, products of metabolic processes from microbial pathogens, and host response to pathological processes such as inflammation and infection can affect the VOCs. Thus, VOCs emanating from exhaled breath may provide a deep insight into various biochemical processes in the human body.[7,8]

Previous studies have shown bacterial pneumonia, reactive oxygen species (ROS), inflammation, septic condition, the use of ventilators, and viral infection can emit different VOC profiles.[7,9] The infection with SARS-CoV-2 is also believed to have a distinguished VOC profile. Analysis of VOCs in the exhaled breath has the potential to become a diagnostic test that is not only quick but also non-invasive, reliable, and widely available.[7]

METHODS

A cross-sectional study was conducted at Saiful Anwar General Hospital, East Java Province, Indonesia, and Idjen Boulevard Field Hospital, Malang, Indonesia. Confirmed cases of COVID-19 patients, regardless of their severity, who were admitted to one of these hospitals were randomly selected and provided informed consent. Subjects with acute deterioration, using invasive ventilation, or being unable to provide exhaled breath samples were excluded. Healthcare professionals with no respiratory symptoms and negative results of RDT or RT-PCR for SARS-CoV-2 were also recruited as healthy subjects for a comparison group. Subjects in the COVID-19 group were further divided into subgroups based on the severity of the disease.

The severity of the disease is classified based on the national guidelines for COVID-19 management in Indonesia. Those without any symptoms were classified as asymptomatic. Mild degree is defined as a patient with symptoms such as cough, fatigue, fever, anorexia, shortness of breath, myalgia, sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, anosmia, and ageusia, without any sign of pneumonia. A moderate degree is marked by pneumonia with room air saturation equal to or above 93%. If the saturation drops below 93%, then it is classified as severe. The critical degree is defined as those with acute respiratory distress syndrome (ARDS), septic shock, or sepsis.

Subjects in both groups were asked to exhale into 500 mL of a sealed airbag. The valve of the airbag is then opened and connected by a tube to the breath analyzer device. This device is equipped with an arrayed sensor to detect the concentration of CO_2, C_7H_8, CH_2O, NH_4, TVOC, NO_2, NH_3, CO, and acetone. The results were obtained within less than 30 minutes, recorded in a customized program, and quantified for further analysis. The concentration of VOCs is compared between COVID-19 and control groups. Further comparisons were also done in the COVID-19 group based on its severity. This study also analyzed the correlation between VOCs and the severity of COVID-19.

RESULTS

A total of 132 participants were included, divided into two groups. Group 1 was the COVID-19 group with 90 confirmed cases of COVID-19 patients. The second group consisted of 42 healthy subjects, defined as the control group.

Table 1. Characteristics of subjects

Characteristics	Group 1 (n= 90)	Group 2 (n= 42)	*P*
Gender			
Male	61 (67.8%)	23 (54.8%)	0.148
Female	29 (32.2%)	19 (45.2%)	
Age			
18-29	27 (30%)	18 (42.9%)	
30-39	9 (10%)	24 (57.1%)	<0.001*
40-49	11 (12.2%)	0 (0%)	
>49	43 (47.8%)	0 (0%)	
Smoking Status			
Never smoker	55 (61.1%)	39 (92.8%)	
Ex-smoker	28 (31.1%)	1 (2.4%)	<0.001*
Active smoker	7 (7.8%)	2 (4.8%)	
Comorbid			
Diabetes Mellitus	14 (15.5%)	1 (2.4%)	0.026*
Cardiovascular Disease	20 (22.2%)	3 (7.1%)	0.033*
Asthma	4 (4.4%)	6 (14.3%)	0.047*
Chronic Obstructive Pulmonary Disease	0 (0%)	0 (0%)	-
Active Tuberculosis	0 (0%)	1 (2.4%)	0.142
Obesity	11 (12.2%)	6 (14.3%)	0.742
Malignancies	0 (0%)	0 (0%)	---
None	55 (61.1%)	27 (64.3%)	0.726

Table 2. Comparison between VOCs of exhaled breath between healthy subjects and COVID-19 subjects

Parameter		N	Mean	SD	Median	*P*
CO_2	Healthy	42	1278.5	610.9472	1175.14	
	COVID-19	90	711.3599	348.57465	607.27	0.0001
	Total	132	891.8136	519.30829	891.21	
C_7H_8	Healthy	42	0.0167	0.06872	0	
	COVID-19	90	0.8791	0.67732	0.93	0.0001
	Total	132	0.6047	0.68973	0.47	
CH_2O	Healthy	42	0.0453	0.10214	0.01	
	COVID-19	90	1.7664	2.01069	0.55	0.0001
	Total	132	1.2188	1.84324	0.28	
NH_4	Healthy	42	0.9996	0.61911	1.05	
	COVID-19	90	1.1749	2.00002	0	0.001
	Total	132	1.1191	1.68651	0.52	
TVOC	Healthy	42	0.4158	0.59951	0.1466	
	COVID-19	90	0.1313	0.20685	0.05	0.0001
	Total	132	0.2218	387.62139	0.080	
NO_2	Healthy	42	1.5615	0.76288	1.54	
	COVID-19	90	0.0441	0.02336	0.04	0.0001
	Total	132	0.5269	0.82817	0.79	
CO	Healthy	42	0	0	0	
	COVID-19	90	0.2298	0.07332	0.24	0.0001
	Total	132	0.1567	0.12326	0.12	
NH_3	Healthy	42	0.6637	0.32482	0.66	
	COVID-19	90	2.08	1.3989	1.99	0.0001
	Total	132	1.6294	1.34202	1.32	
ACET	Healthy	42	0.2279	0.1536	0.23	
	COVID-19	90	1.0751	1.99449	0	0.001
	Total	132	0.8055	1.69319	0.11	

Note: CO_2=carbon dioxide; C_7H_8=Toluene; CH_2O=Formaldehyde; NH_4=Ammonium; TVOC=Total Volatile Organic Compounds; NO_2=Nitrogen dioxide; CO=Carbon monoxide; NH_3=Ammonia; ACET=Acetone

Table 3. Correlation of VOCs between subgroups based on disease severity in COVID-19 group

VOCs	Degree of severity	Median (Min-Max)	Mean±SD	*P*
CO_2	Asymptomatic	603.4 (462.67-1673.9)	---	
	Mild	711.8 (400-1876.5)	---	
	Moderate	612.83 (400-747.73)	---	0.002*
	Severe	548.27 (400-1443.4)	---	
	Critically ill	431.03 (400-1246.2)	---	
TVOC	Asymptomatic	0.09 (0.02-0.836)	---	
	Mild	0.11 (0-0.709)	---	
	Moderate	0.02 (0-0.15)	---	0.0001*
	Severe	0.02 (0-0.194)	---	
	Critically ill	0.01 (0-0.071)	---	
CO	Asymptomatic	---	0.14±0.06	
	Mild	---	0.20±0.07	
	Moderate	---	0.28±0.03	0.0001*
	Severe	---	0.27±0.05	
	Critically ill	---	0.28±0.04	
NH_3	Asymptomatic	---	1178.89±634.10	
	Mild	---	971.46±644.57	
	Moderate	---	1398.91±289.86	0.043*
	Severe	---	1232.86±428.48	
	Critically ill	---	1250.63±392.80	
NH_4	Asymptomatic	0 (0-10.19)	---	
	Mild	0 (0-3.43)	---	
	Moderate	0.12 (0-3.94)	---	0.0001*
	Severe	1.43 (0-6.64)	---	
	Critically ill	1.625 (0-5.8)	---	
ACET	Asymptomatic	0 (0-8.17)	---	
	Mild	0.00 (0-1.64)	---	
	Moderate	0.27 (0-5.30)	---	0.002*
	Severe	0.47 (0-6.35)	---	
	Critically ill	0.96 (0-6.52)	---	
NO_2	Asymptomatic	---	0.06±0.02	
	Mild	---	0.04±0.02	
	Moderate	---	0.04±0.03	0.275
	Severe	---	0.04±0.03	
	Critically ill	---	0.04±0.02	
C_7H_8	Asymptomatic	1.525 (0.09-2.54)	---	
	Mild	0.16 (0.01-1.72)	---	
	Moderate	1.105 (0-1.82)	---	0.243
	Severe	0.92 (0-2.14)	---	
	Critically ill	1.015 (0-1.59)	---	
CH_2O	Asymptomatic	4.4 (0-7.16)	---	
	Mild	0.02 (0-5.14)	---	
	Moderate	0.27 (0-3.02)	---	0.100
	Severe	1.49 (0-4.64)	---	
	Critically ill	2.245 (0-4.71)	---	

Note: CO_2 and TVOC show a negative correlation; CO, NH_3, NH_4, and ACET show a positive correlation; NO_2, C_7H_8, and CH_2O show no correlation

Group 1 was further divided based on its severity, 12 (13.3%) subjects were asymptomatic, 33 (36.7%) subjects had mild disease, 10 (11.1%) subjects had moderate disease, 23 (25.6%) subjects had severe disease, 12 (13.3%) subjects were critically ill. Nine parameters of VOCs from exhaled breath samples were compared between group 1 and group 2. In COVID-19 groups, we obtained a

significantly higher concentration of C_7H_8, CH_2O, CO, and NH_3 when compared to the control group (respectively 0.92 vs 0.0; 0.55 vs 0.01; 0.24 vs 0.0; 1.99 vs 0.67; all with a P<0.05). While for the other markers, the concentration was significantly lower, including CO_2, NH_4, TVOC, NO_2, and acetone, in COVID-19 groups (respectively 607.3 vs 1175.1; 0.0 vs 1.05; 0.05 vs 146.6; 0.04 vs 1.55; 0.0 vs 0.23; all with a P<0.05).

Further comparisons in the COVID-19 group were carried out to analyze the difference between VOCs concentration based on the severity of the diseases. Only six markers showed differences. CO (P=0.0001), CO_2 (P=0.002), NH_4 (P=0.0001), NH_3 (P=0.043), Acetone (P=0.002), and TVOC (P=0.0001) were significantly different between subgroups based on disease severity. The severity of the disease was also correlated with the concentration of those markers. The positive correlations were observed in NH_4, Acetone, CO, and NH_3 with correlation coefficients of 0.476, 0.358, 0.645, and 0.236, respectively, while the negative correlations were seen in CO_2 and TVOC with correlation coefficients of -0.407 and -0.574.

DISCUSSION

Although studies related to the content of human breath have been conducted a long time ago, with the first study recorded in the period 1777-1783 by Lavoisier, research in this medical field has not developed widely.[9] Using one of the VOCs as a biomarker of disease is generally insufficient because of its complexity and heterogeneity, including environmental exposures and the presence of chronic diseases. Detecting VOCs in exhaled breath has the potential to be used as a diagnostic tool or a large-scale screening modality. Rather than detecting one VOC as a marker for one disease, using a set of VOCs and finding its pattern to create a “fingerprint” or “breath-print” is the preferred approach.[10] This study found that a set of VOCs consisting of C_7H_8, CH_2O, CO, NH_3, CO_2, NH_4, TVOC, NO_2, and acetone was able to differentiate between COVID-19 patients and healthy subjects.

Continuous monitoring of exhaled CO_2 is a method to ensure adequate ventilation during mechanical ventilation. The volume of CO_2 excreted by the cardiorespiratory system is a sensitive indicator of not only ventilation efficiency but also pulmonary perfusion and cardiac output.[11] Based on the Enghoff-Bohr equation, a lower concentration of CO_2 can reflect the condition of increased dead space, ventilation–perfusion mismatch, and ARDS. Those conditions usually occur in COVID-19 and are usually associated with its severity.[12] The low concentration of CO_2 in our research may be caused by those conditions. Using a metabolic analyzer and volumetric capnography are preferable methods to measure CO_2 concentration and predict partial pressure of the mean expired CO_2.[11]

Higher concentrations of NH_3 and lower concentrations of NH_4 in COVID-19 patients, as well as a positive correlation with the degree of severity, may occur as a result of lower pH in the respiratory airway, acidification by gastric fluid, and influence of nitrite or nitrate metabolism by respiratory or gastrointestinal bacteria.[13,14] Previous studies of the airway pH of patients with ARDS failed to document acidification, although these patients had acidopnea.[13] Lower pH in the esophagus showed a higher expression of angiotensin-converting enzyme 2 (ACE2).[15] Higher expression of ACE2 may be responsible for the increased severity of COVID-19 and the risk of death from COVID-19.[15,16]

The cytochrome P450 (CYP) expression and activity are greatly affected by an immune response and altered during COVID-19 infection.[17] The altered activity of CYP may lower the metabolism of C_7H_8 (toluene), causing higher excretion of toluene in exhaled breath.[18] Intracellular pro-oxidant/antioxidant imbalance leads to oxidative stress, resulting in lipid peroxidation.[19] Oxidative stress occurred during

COVID-19, and increased levels of activated neutrophils increased the production of CH_2O.[20,21] Oxidative stress also induces heme oxygenase-1 (HO-1) activity in the airway, nasal epithelium, alveolar macrophages, endothelial cells, and other lung cell types, thus endogenously producing CO.[22] The concentration of CO also increases during infection, neutrophilic inflammation, and other critical conditions requiring mechanical ventilation.[23] Similar to CO, acetone may also increase as a result of infection, septicemia, and critically ill conditions.[24] Treatment given during COVID-19 may also affect the concentration of VOCs. Antioxidants such as vitamin E and vitamin C, which are given in all COVID-19 subjects, are known to reduce the level of NO_2.[25]

LIMITATION

This study has some limitations. The first limitation is that a sensor-based analyzer can only calculate one type of VOC concentration per sensor. Thus, targeted VOCs are already predetermined, and other VOCs that may be pathognomonic for a disease remain undetectable. The second limitation is many things can affect the results of research related to VOC. Variations of the sampling process and environmental influences such as exogenous VOCs, humidity, and temperature cannot be fully controlled. This may cause differences in results between one study and another.

CONCLUSION

COVID-19 affects many aspects of the human body and causes an alteration in the composition of VOCs in exhaled breath. Our study shows there are differences in several VOC concentrations that can differentiate between COVID-19 patients and healthy subjects. Those distinctive profiles can be used as a method of diagnosing COVID-19 that is fast, reliable, and without risk of complications. Disease severity is also known to affect changes in VOC concentrations. With this discovery, VOC concentration may be expected to be a prognostic biomarker in the future, as it is known that the severity of the disease in COVID-19 affects the patient's prognosis, although further research is required.

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CONFLICT OF INTEREST

None.

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REFFERENCE

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Original Article

Clinical Performance of the *Aspergillus* Western Blot IgG Kit for Serodiagnosis of Chronic Pulmonary Aspergillosis in Post-Tuberculosis Patients

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Abstract

Background: Chronic pulmonary aspergillosis (CPA) by *Aspergillus* spp., which causes slowly progressive destruction of lung parenchyma, is a major complication of pulmonary tuberculosis (TB). Clinical and radiological features of CPA are not typical and might resemble TB. Therefore, detecting *Aspergillus*-specific IgG is critical for diagnosing CPA.

Methods: This cross-sectional study was conducted to evaluate the performance of the *Aspergillus* Western Blot (Asp-WB) IgG kit (LDBio Diagnostics, Lyon, France) for CPA diagnosis in 63 post-TB patients. The analysis was performed by comparing Asp-WB with *Aspergillus* ELISA IgG (Asp-ELISA) and fungal culture as the standard method.

Results: Of the 63 patients studied, twenty-six (41%) met the probable CPA criteria. The Asp-WB results were positive in 13 probable CPA patients and 3 non-CPA patients, with a significant difference of 50% vs. 8% (P<0.001). The sensitivity and specificity of Asp-WB were 50% and 93%. False-negative results of Asp-WB were detected from non-fumigatus CPA that grew *Aspergillus niger*. CPA patients with mild symptoms (less than 3 months) indicated early progression of CPA might show positive Asp-WB test results in low sensitivity of Asp-WB test.

Conclusion: The Asp-WB has the potential to be used as a confirmatory test to assist diagnosis of CPA in post-TB patients.

Keywords: chronic pulmonary aspergillosis, tuberculosis, Western blot

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INTRODUCTION

Pulmonary tuberculosis (PTB) remains a serious problem in Indonesia. About 8.5% of global TB cases occurred in Indonesia, a country with the second-highest TB burden in the world.[1] Pulmonary TB may damage lung tissue, making it easier for the adhesion and invasion of *Aspergillus,* which can lead to chronic pulmonary aspergillosis (CPA) in certain cases.[2–6] It affects approximately 1.2 million individuals with CPA as a sequel of PTB.[7]

The prevalence of CPA is estimated at 378,700 cases in Indonesia.[8] The incidence rate of CPA at the end of TB therapy in the previous study was 8%.[9] The CPA diagnosis is still challenging because of the atypical clinical manifestations, radiology findings and low sensitivity of the fungal culture. Detection of antibodies against *Aspergillus* might facilitate an accurate diagnosis of CPA. The prior study categorized the diagnosis of CPA into probable and proven CPA. Probable CPA may represent early-stage CPA or limited radiology information due to lack of thorax CT scan, so the lung cavity is undetectable.

The enzyme-linked immunosorbent assays (ELISAs) and immunoprecipitation detection (IPD) are widely used to detect specific anti-*Aspergillus* antibodies.[10–13] However, those tests have drawbacks, including time-consuming, lack of standardization, and extended turnaround times. The *Aspergillus* Western Blot IgG kit (*Asp*-WB) has been commercialized (LDBio Diagnostics, Lyon, France) using *A. fumigatus* glycoprotein antigen with a molecular weight of 16 kD, 18-20 kD, 22 kD, and 30 kD.[14–16] Study on Asp-WB for diagnosing of CPA are still limited in Indonesia. This study aimed to evaluate

the accuracy of Asp-WB compared to consensus results of fungal cultures and Asp-ELISA to support CPA diagnosis in post-TB patients.

METHODS

This cross-sectional study is part of the prior study on CPA diagnostics in Indonesia. Clinical material was obtained from the sera of post-TB patients from several hospitals in Jakarta, which were delivered to the Parasitology Laboratory FMUI. The previous study recruited patients by consecutive sampling in April-December 2019.

Inclusion criteria were previous TB patients who had persistent symptoms after completing TB therapy and negative HIV tests. Probable CPA was diagnosed based on three parameters: 1) *Aspergillus* culture positive and/or positive *Aspergillus* antibody test including immunochromatography (ICT) or Western Blot (WB) methods, and 2) at least one of these symptoms including cough, dyspnoea, chest pain, hemoptysis, and/or fatigue within ≥3 months, OR 3) radiological features indicative of CPA (at least one of cavitation and/or fungal ball)**.** The study was performed at the Parasitology Laboratory, FMUI. It was approved by the Health Research Ethics Committee of FMUI through the Ethics Review No. 95/UN2.F1/ETIK/2019.

Aspergillus Western Blot IgG test: 1,2 ml of buffer solution was added to each incubation tray with a strip in it. Samples and control were added by 10 µl and incubated for 90 minutes. The solution was washed with buffer solution (1:10) three times. Then, 1,2 ml of anti-IgG conjugate was added and incubated for 60 minutes. The solution was rewashed, and 1,2 ml of substrate was dispensed depending on the strip coloration and incubated for 60 minutes. The strips were left to dry for at least 15 minutes at room temperature.

The results were contrasted with the positive control and determined as positive or negative according to the manufacturer. *Aspergillus*-specific sensitization was proved by four protein bands at 16, 18 to 20, 22, and 30 kDa. The result was positive when at least two of these bands were documented (Figure 1A). The Asp-WB global intensity was scored from 1 to 4 by summing the results of each specific band (Figure 1B). Asp-WB intensity was classified as very high (>10), high (5 to 10), moderate (2 to 4), and weak (<2). Each test was carried out in duplicate and read by two experts.[16]

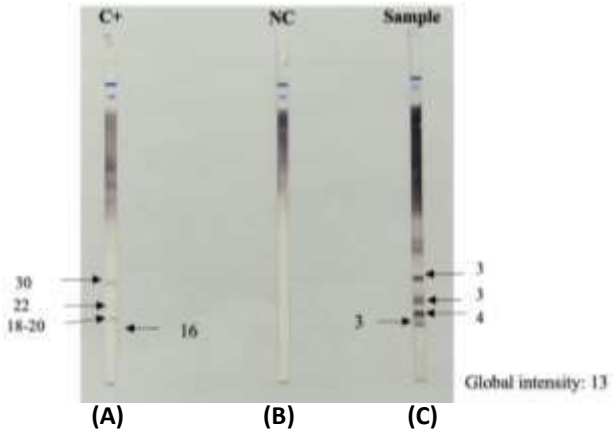

Figure 1. *Asp*-WB results.
(A) C+ positive control; the mass (in kDa) of the specific bands shown by values next to the arrows. (B) NC, negative control. (C) Quantification of *Asp*-WB band intensity in a positive assay; the intensities of four specific bands were 3, 3, 4, and 3, respectively, yielding a global intensity of 13.

Aspergillus ELISA IgG test: The sera were tested using the IgG-specific *Aspergillus* antibody with an indirect ELISA method. As 100 µl diluted sample, standard and controlled solutions were taken by pipets, then put in the well and incubated for 60 minutes. The solution was washed three times with washing solution (1:20). Anti-IgG conjugate was added to the solution and incubated for 30 minutes. The solution was rewashed and a substrate solution was added. It was incubated for 15 minutes, and then a stopping solution was added. It was interpreted by using an ELISA reader with 450 nm wavelength which resulted in a cut-off positive result ≥120 AU/ml, negative <80 AU/ml, and inconclusive 80-110 AU/ml.

Diagnostic potential in this study was assessed based on the sensitivity test and specificity test. Data were presented using frequencies and percentages for binary and categorical variables. Fisher's exact tests or chi-squared tests were used for categorical variables. Statistical analysis was performed by using IBM SPSS 22 statistic software.

RESULTS

Sixty-three sera from post-TB patients were included in the study (Table 1). Twenty-six (41%) out of 63 patients met the criteria for probable CPA. The main symptoms in the probable CPA cases were dyspnoea (n=10, 38%) and fatigue (n=10, 38%).

Table 1. Demography of post-TB patients

Symptoms	ALL (n=63)	CPA (n=26)	Non-CPA (n=37)	*P*
Gender				
Male	42 (67%)	19 (73%)	23 (62%)	
Female	21 (33%)	7 (27%)	14 (38%)	0.366
Mean age (range in years)				
≥ 60 years	16 (25%)	7 (27%)	9 (24%)	
< 60 years	47 (75%)	19 (73%)	28 (76%)	0.816
Sign & symptoms (>3 months)				
Cough	19 (30%)	9 (35%)	10 (27%)	0.518
Haemoptysis	11 (18%)	4 (15%)	7 (19%)	1
Dyspnoea	22 (35%)	10 (38%)	12 (55%)	0.621
Chest pain	10 (16%)	4 (15%)	6 (16%)	1
Fatigue	26 (41%)	10 (38%)	16 (43%)	0.704

Among 63 patients, the strong positive and weak positive rates of Asp-WB tests were 13% (n=8) equally, with a total result of 25% (n=16) positives. In the probable CPA group, 13 of 26 sera tested had positive results by Asp-WB with 50% sensitivity. In the non-CPA group, 34 of the 37 sera showed negative results by WB with 92% specificity. The Asp-WB results were positive in 13 probable CPA patients and three non-CPA patients, with a significant difference of 50% vs. 8% (P<0.001). Fifteen percent (n=4) of the probable CPA group showed three bands in the Asp-WB test, which is significantly higher compared to none patients (0%) in a non-CPA group (P=0.025).

Table 2. The result of Asp-WB based on antigen characterization

Antigen characterization (molecular weight)	Total (n=63)	CPA (n=26)	Non-CPA (n=37)	*P*
16 kD	19 (30%)	13 (50%)	6 (16%)	0.004
18-20 kD	17 (27%)	12 (46%)	5 (14%)	0.004
22 kD	10 (16%)	9 (35%)	1 (3%)	0.001
30 kD	9 (14%)	7 (27%)	2 (5%)	0.026

The 16 kDa WB band was the most prevalent (30%) band among 63 patients (Table 2). The proportion of all four WB bands (50% vs. 16% for 16 kDa, 46% vs. 14% for 18–20 kDa, 35% vs. 3% for 22 kDa and 27% vs. 5% for 30 kDa) was significantly higher in the CPA group than in non-CPA group (P<0.05 in all the bands).

The Asp-ELISA and Asp-WB tests require sensitivity and specificity values to become proper diagnostic tools. The tests should possess good accuracy, precision, and reliability. The sensitivity and specificity of Asp-ELISA and Asp-WB are comparable to the combination methods (fungal culture results and positive Ab detection, either with one or both methods) as a standard diagnostic method. The diagnostic accuracy of the Asp-WB kit generally showed a sensitivity (88%) and specificity (94%), whereas other studies reported a sensitivity of 80%. Variations in those results may occur due to differences in population and study design.

DISCUSSION

The evaluation of Asp-WB test performance to diagnose CPA in post-TB patients has been carried out in this study. The assay showed 50% sensitivity and 92% specificity for diagnosis of probable CPA. The relatively lower sensitivity compared to prior studies might be related to different populations and the criteria applied to diagnose CPA.[15]

A previous study that included 88 post-TB patients with negative GeneXpert showed 80% sensitivity and 70% specificity of the Asp-WB test to diagnose proven CPA.[15] The Asp-WB test showed high specificity with only three false positives. These three patients had weak positive bands of the Asp-WB test, but the radiology findings and the symptoms did not meet the criteria of CPA.

However, the growth of *Aspergillus* was documented in the sputum of those three patients; one patient had *A. flavus*, one patient had *A. niger*, and one patient had *A. flavus* and *A. niger*. All these patients presented to the clinic with pulmonary symptoms such as cough, dyspnoea, and chest pain, but in less than three months. The presence of minimal symptoms might indicate the early stage of CPA.

Eight out of thirteen patients with false negative Asp-WB test had *A. niger* in their culture. *Aspergillus*

niger was solely found in five patients, while *A. niger* grew together with *A. flavus* and *A. fumigatus* in three patients. A previous study revealed 38% of *Aspergillus* section *Nigri* as the etiology of CPA in Indonesia.[17] All available Asp-antibody detection kits now are based on the *A. fumigatus* antigen.[14] Therefore, these eight patients appeared as false negative results were likely because of the presence of antibodies specific to non-fumigatus infections (for example *A. niger*). These types of antibodies were undetected by the Asp-WB test that was specific for *A. fumigatus* infection.

The Asp-WB test is part of the diagnostic scheme, as the point-of-care test (POCT) of CPA, particularly in limited-resource settings. The Asp-WB test was then less popular for routine use as POCT due to several issues, including the limitation of ELISA facilities and less economical costs.

Further development of CPA diagnostic tests is by using the lateral flow assay (LFA) method. The test becomes more feasible for POCT of CPA since it is relatively simple, fast and inexpensive. The LFA-based test is more suitable for routine CPA screening. Meanwhile, the high specificity of the Asp-WB test makes it more feasible for confirmatory tests of CPA. The serial Asp-WB test also has more potential for assessing the disease course of CPA, as well as evaluating treatment, following the clinical judgment.

LIMITATION

The limitation of this study includes the lack of serial Asp-WB tests and the availability of thorax CT-scan. Chest x-ray was performed to detect suggestive CPA findings which might not be as reliable as a CT scan in identifying the cavities.

CONCLUSION

In conclusion, the clinical and radiological appearances of CPA might resemble TB. Therefore, an antibody test such as the Asp-WB test is critical to assist in the diagnosis of CPA. The specificity of the Asp-WB test is high, so this test can be used as a confirmatory test to diagnose CPA.

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CONFLICT OF INTERESTS

There is no conflict of interest.

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Original Article

Chest Radiography and CT Scan as Predictor Factors for Long COVID

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Abstract

Background: Long COVID presents a significant challenge in the management of COVID-19 patients, necessitating risk stratification and early intervention to mitigate its impact.

Objective: This retrospective cohort study aimed to establish a predictive link between initial clinical assessments and imaging findings upon COVID-19 diagnosis and the subsequent development of long COVID symptoms at 6-8 weeks post-treatment.

Methods: The study analyzed chest radiography images utilizing the Brixia Score and chest CT scans employing the Severity Score at the time of COVID-19 diagnosis. These findings were then compared with the presence of long COVID symptoms.

Results: Among 54 study participants, 63% were non-elderly and 37% were elderly, with a nearly equal gender distribution. Notably, 74.1% of patients developed long COVID symptoms. The Brixia Score identified 38.9% as mild, 37% as moderate and 24.1% as severe lung involvement. Correspondingly, the Severity Score from chest CT scans revealed 33.3% with mild, 53.7% with moderate, and 13% with severe lung abnormalities. Statistical analysis confirmed strong correlations between both the Brixia Score (r=0.553) and the Severity Score (r=0.733) with the development of long COVID symptoms (*P*=0.0001).

Conclusion: This study underscores the significant predictive value of both the Brixia Score and the Severity Score in identifying COVID-19 patients at risk of developing long COVID. These findings have critical implications for early risk stratification and targeted intervention strategies to prevent long COVID's debilitating effects.

Keywords: Brixia, COVID-19, long COVID, severity score

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INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is an infectious disease caused by the novel coronavirus, which since December 2019 has spread from China to the rest of the world and was declared a global pandemic by the World Health Organization (WHO) on March 11th, 2020. This infection can cause severe pneumonia and even fatal acute respiratory syndrome.[1]

The spectrum of infection severity ranges from asymptomatic to mild, which is observed in a total of 81% of cases; moderate symptoms (14% of total cases) with shortness of breath, hypoxia, or involvement of more than half of the lung on chest radiograph; severe (5% of cases) with respiratory failure, shock, or multiorgan dysfunction.[2] The mortality rate in the world is 2.38% for reported non-critical cases. Severe disease can occur in healthy people of all ages but is most commonly found in the elderly or patients with co-morbidities such as cardiovascular disease, diabetes mellitus, hypertension, chronic pulmonary disease, lung cancer, malignancy, metastatic disease, chronic kidney disease, obesity and tobacco-related diseases.[2]

Laboratory findings related to severity include lymphopenia, thrombocytopenia, neutrophil-lymphocyte ratio >3.3; increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT) (37%), lactate dehydrogenase (LDH), increases inflammatory markers such as C-Reactive

Protein (CRP), ferritin, D-dimer (>1 mcg/ml), prothrombin time, troponin, creatinine phosphokinase, and acute renal failure.[2] Although chest radiography is considered insensitive for detecting lung involvement in its early stages, in emergencies, standard or bedside chest radiography becomes an important diagnostic tool for monitoring the day-to-day development of unstable lung conditions in COVID-19, especially in critical conditions (ICU patients).[3]

Long COVID is a condition where the patient does not recover after several weeks or months after getting the initial symptoms of COVID-19, regardless of whether they are examined or not.[4] Many COVID-19 patients who are hospitalized still experience further symptoms such as shortness of breath, coughing, fatigue, and mental disorders. In many cases, not only severe COVID-19 cases but also mild cases have recurring symptoms including constant fatigue, headaches, chest pains, myalgias, palpitations, and even cognitive impairments such as poor memory and concentration.[4]

WHO defines "long COVID" or "post-COVID-19 syndrome" as characterized by the persistence of symptoms in individuals who have had confirmed or probable SARS-CoV-2 infections. This condition is defined as the presence of symptoms lasting for at least two months, with an initial onset occurring within three months of the acute COVID-19 infection.[5]

Commonly reported symptoms include fatigue, an altered sense of smell (anosmia), and anxiety, although other symptoms have also been documented. These lingering symptoms significantly affect daily functioning, impacting areas such as eating habits, physical activity, behavior, academic performance, social interactions with friends and family, and developmental milestones.[5]

Symptoms may either appear anew after initial recovery from acute COVID-19 or continue from the initial illness, exhibiting fluctuations or relapses over time. It is worth noting that while further diagnostic investigations may identify additional medical conditions, the presence of such conditions does not negate the diagnosis of post-COVID-19 conditions, underscoring the complexity of managing these cases and the need for ongoing research and clinical care.[5]

In the majority of patients recovering from severe COVID-19, significant pulmonary fibrosis is found. Chest radiography is used to diagnose and evaluate disease progression in the lungs. However, follow-up chest radiography did not correlate with abnormal CT findings or permanent functional impairment. Chest radiography is an independent risk factor for poorer prognosis in COVID-19 patients, where 86% have an abnormal Chest CT after 3 months. In this study, changes in Chest radiography findings were correlated with recovery time, and abnormal findings were reported to be significantly correlated with COVID-19 severity.[6]

METHODS

This study was conducted at Budhi Asih Hospital between December 2021 and May 2022. We enrolled 54 consecutive patients (28 males and 26 females) in a retrospectively designed study. The inclusion criteria were adults over 18 years old with a history of hospitalization due to moderate, mild, or severe COVID-19 conditions, a current PCR of negative result, and a complete Chest X-ray and Chest CT when admitted to the hospital. Patients with massive pleural effusion and pneumothorax were excluded.

All data from the study sample were identified and recorded, including all symptoms for 6-8 weeks after hospitalization. Initial chest radiographs were analyzed using the Brixia score, while initial chest CTs were analyzed using the severity score. This study was designed as a retrospective cohort to analyze chest radiography using the Brixia score and chest CT scan using the severity score from the initial findings. The result will be used as a predictor of long COVID.

Chest radiography was performed on a mobile digital x-ray machine (Mobilett Elara Max, Siemens, Forchheim, Germany). The patient is positioned upright or supine, with the trachea centered and equidistant from the clavicular heads on either side,

the spine visible as a transparent structure through the cardiac shadow, and a full inspiratory effort if possible. Standard exposure parameters are 80 kVp and 2 mAs.

Chest CT was performed without contrast administration on a 128-multislice detector CT system (Revolution Maxima, GE, Waukesha, Wisconsin). All patients were positioned supine (headfirst, arms above head) right at the isocenter of the gantry. The scanning range extends from the level of the tracheal bifurcation to the diaphragm. The following scan parameters were used: 2x64x0.625 mm detector collimation with resulting slice acquisition of 2x128x0.625 mm via a z-flying focal point, 280 msec gantry rotation time, and 3.4 pitch. This study was approved by the local ethical committee, and informed consent was obtained from all patients.

RESULTS

Table 1 depicts an almost equal proportion of age, gender, and comorbid characteristics. However, the proportion of characteristics based on lab results shows a greater proportion of abnormal lab results.

Table 1. Frequency Distribution of Patient Characteristics

Characteristics	n	%
Age		
Non-elderly	34	63.00
Elderly	20	37.00
Gender		
Women	26	48.10
Man	28	51.90
Comorbid		
No	29	53.70
Yes	25	46.30
Lab Result (PCR, NLR)		
Normal	2	3.70
Abnormal	52	96.30

Table 2. Frequency Distribution of Variable

Variable	n	%
Brixia Score		
Mild	21	38.9
Moderate	20	37.0
Severe	13	24.1
Severity Score		
Mild	18	33.3
Moderate	29	53.7
Severe	7	13.0
Long COVID symptoms		
No	16	29.6
Yes	38	70.4

Whereas in Table 2, it was observed that most subjects had mild Brixia Score (38.9%), moderate Severity Score (53.7%), and long COVID symptoms (70.4%) people with a severe Severity Score (13.0%).

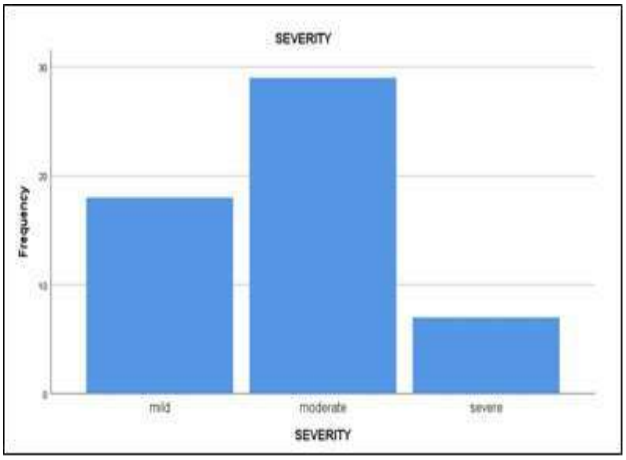

Figure 1. Severity Score

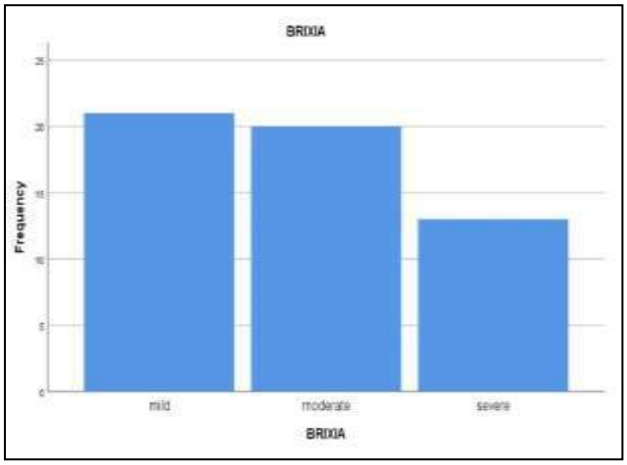

Figure 2. Brixia Score

Figure 1 shows that there are more moderate Severity Scores than mild and severe. Figure 2 shows that the mild Brixia Score is higher than the moderate and severe.

Table 3. Brixia Score and Severity Score for Long COVID Symptoms (N=54).

Variable	Long COVID symptoms		Total	r	*P*
	No	Yes			
Brixia Score					
Mild	13	8	21		
Moderate	3	17	20	0.553	0.0001
Severe	0	13	13		
Severity Score					
Mild	15	3	18		
Moderate	1	28	29	0.733	0.0001
Severe	0	7	7		

In Table 3, it can be concluded that the correlation between the Brixia score and long COVID

symptoms has r=0.553 with a strong relationship, and *P*=0.0001 which means there is a correlation. The correlation between severity score and long COVID symptoms has r=0.733 with a strong relationship, and *P*=0.0001 which means there is a relationship. It can be concluded that the higher the results of the Brixia score and severity score, the higher the long COVID symptoms.

DISCUSSION

The correlation between the Brixia score and severity score for long COVID symptoms shows a strong relationship (Table 3). The Brixia score correlates strongly with disease severity and outcome and also can support clinical decision-making.[7] It can even determine the fatality of a disease that results in death if the score is higher than 12.[8] Although the Brixia score can predict mortality, it cannot predict the length of stay of confirmed COVID-19 patients who are hospitalized.[9,10]

LIMITATION

This study used retrospective data so the data obtained was less comprehensive. There was a potential for bias in the data because the patient's symptoms were subjective. There was also the possibility of other co-morbidities outside those studied, thus disguising the symptoms of long COVID itself.

CONCLUSION

There is a significant relationship between Brixia score based on chest radiography and long COVID symptoms. There is also a significant correlation between severity scores based on chest CT scans and long COVID symptoms. Researchers feel the need to dig deeper into the symptoms of long COVID patients, supplemented by radiological images with chest CT scan modalities and chest radiography, which can be used to predict long COVID patients.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

There is no conflict of interest.

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Original Article

Differences in C-reactive Protein Level Based on Clinical Severity and Outcome of COVID-19 Patients at Dr. M. Djamil Hospital, Padang

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Abstract

Background: Inflammatory processes in COVID-19 can increase inflammatory markers such as C-reactive protein (CRP), procalcitonin (PCT), and interleukin 6 (IL-6). The level of C-reactive protein describes the severity of viral infection. Several studies have been conducted to investigate the link between C-reactive protein levels and the severity of COVID-19. The purpose of this study is to identify differences in C-reactive protein levels based on clinical degrees and outcomes of COVID-19 patients treated at Dr. M. Jamil General Hospital, Padang.

Methods: This is a retrospective cohort study that analyzed all COVID-19 patients treated at Dr. M. Jamil General Hospital, Padang. This study lasted from December 1st, 2021 and June 1st, 2022. The data was analyzed using univariate, bivariate, and confounding analysis. Bivariate analysis explored differences in C-reactive protein levels in clinical severity and patient outcomes for COVID-19. The Kruskal-Wallis test determined the difference between the CRP level and clinical severity, while the Mann-Whitney test determined the difference between the CRP level, length of stay and final hospitalization status. The confounding test was performed using multiple linear regression tests.

Results: The majority of participants were women (51.0%) with a range of age between 50–59 years (28.0%) and suffered from hypertension (46.0%). Less than half of them had secondary infection (49.0%). The majority of them had a critical clinical severity (75.0%) and length of stay ≤14 days (77.0%) and more than half were deceased (65.0%). C-reactive protein levels were higher in patients with critical clinical degrees (89.00 mg/L) compared to moderate (37.50 mg/L) and severe (23.00 mg/L), C-reactive protein levels in patients with long hospitalization ≤14 days (97.00 mg/L) was higher than >14 days (88.50 mg/L), and C-reactive protein levels were higher in patients who died (93.00 mg/L) than those who survived (68.00 mg/L).

Conclusion: C-reactive protein levels differed significantly based on clinical severity, length of stay and end of stay status of COVID-19 patients.

Keywords: C-reactive protein, COVID-19, clinical severity

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 will bind to Angiotensin Converting Enzyme 2 (ACE2) receptors in target organs such as the lungs, heart, renal system, and gastrointestinal system.[1,2]

The COVID-19 clinical manifestations include asymptomatic, mild, moderate, severe, or multi-organ dysfunction caused by the inflammatory process of viral infection. The inflammatory process increases inflammatory markers such as C- reactive protein (CRP), procalcitonin (PCT), and interleukin 6 (IL-6) (IL-6).[1,2]

The study by Liu et al on 140 COVID-19 patients found elevated levels of IL-6 in 95 patients (67.9%), C-reactive protein in 91 patients (65.0%), and procalcitonin in 8 patients (5.7%).[3] Zeng et al reported an association between elevated inflammatory markers and severity of COVID-19 patients in their meta-analysis. Monitoring the rise in these inflammatory markers can facilitate in determining the severity and prognosis of COVID-19 disease.[4]

C-reactive protein is a highly sensitive systemic marker that can be used as an indicator of inflammation during the acute phase of inflammation, infection, and tissue damage.[5] Hepatocytes produce C-reactive protein, which is secreted 4-10 hours after inflammation. C-reactive protein levels peak after 48

hours of inflammation and have a half-life of 19 hours.[6] C-reactive protein normal values vary. In suspected cases of COVID-19 with fever and respiratory symptoms, CRP level of 4 mg/L has proven useful as triage.[7]

C-reactive protein levels indicate the severity of viral infection. According to Chen et al study, the average amount of C-reactive protein in COVID-19 patients with severe clinical symptoms was higher than in those without severe clinical symptoms.[6] A mild viral illness is indicated by slightly elevated C-reactive protein levels (10–20 g/mL). COVID-19 patients with moderately elevated C-reactive protein levels (>20-40 g/mL) may experience reversible tissue damage as a natural response to the disease. COVID-19 patients with significantly elevated C-reactive protein levels (>100 g/mL) have advanced tissue damage, coagulation abnormalities, and multipleorgan failure, all of which are associated with a life-threatening prognosis.[7]

Several studies have been conducted to investigate the association between C-reactive protein levels and the severity of COVID-19. Tan et al.found a significant increase in C-reactive protein levels in 27 COVID-19 patients in the early stages of the disease in their study involving 27 COVID-19 patients in China. High levels of C-reactive protein are associated with extensive lesions in the lungs, according to computed tomography (CT) analysis of disease severity. In this study, C-reactiveprotein is associated with disease progression and can be used to predict the initial severity of COVID-19 disease.[8]

According to Chen et al study, high levels of C-reactive protein were associated with severe pneumonia and longer duration of illness than low levels of C-reactive protein. C-reactive protein has also been used in several studies to predict inpatient mortality and the need for mechanical ventilation.[9] High levels of C-reactive protein were associated with systemic inflammation and also strongly associated with venous thromboembolism (VTE), acute kidney injury (AKI), the severity of critical illness, and death in COVID-19 patients, according to a study conducted bySmilowitz et al. in New York involving adult patients with confirmed COVID-19.[10]

Based on the information presented above, the authors were interested in investigating differences in C-reactive protein levels based on clinical degrees and outcomes of COVID-19 patients who were treated at Dr. M. Djamil General Hospital, Padang.

METHODS

This was a retrospective cohort study. The study was conducted from December 2021 to June 2022 in the COVID-19 isolation room at Dr. M. Djamil General Hospital, Padang. All COVID-19 patients treatedat Dr. M. Djamil General Hospital, Padang between January 1st, 2021, and December 31st, 2021 who met the inclusion and exclusion criteria were included in this study.

The results of RT-PCR/TCM SARS-CoV-2 taken from nasal or nasopharyngeal swabs of patients aged 18 years, as well as complete medical record data including name, age, sex, comorbidities, clinical degree, protein levels (C-reactive), and outcomes of COVID-19 patients, were used to determine study inclusion criteria. Patients with high C-reactive protein levels who were evaluated qualitatively were excluded from the study.

RESULTS

There were 100 participants who met the criteria for inclusion and exclusion. The characteristics of COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang are shown in Table 1. The majority of patients were female (51.0%) with age ranges between 50-59 years (28.0%). Hypertension (46.0%) and diabetes (34.0%) were the most prevalent comorbid. Secondary infections were found in 49.0% of participants. The majority of participants (75.0%) had a critical clinical degree and length of stay less than 14 days (77.0%) and more than half of them were deceased (65.0%) (Table 1).

Table 2 shows that patients with critical severity had higher levels of C-reactive protein (89.00 mg/L) than those with moderate (37.50 mg/L) or severe (23.00 mg/L). The analysis revealed significant differences in C-reactive protein levels based on the clinical severity of COVID-19 patients

being treated at Dr. M. Djamil General Hospital, Padang (*P*=0.006).

Table 1. Characteristics of COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Variable	N (%)
Age (Years)	
<50	21 (21.0%)
50–59	28 (28.0%)
60–69	27 (27.0%)
≥70	24 (24.0%)
Gender	
Male	49 (49.0%)
Female	51 (51.0%)
Comorbid	
Cerebrovascular	4 (4.0%)
Hypertension	46 (46.0%)
Diabetes Mellitus	34 (34.0%)
Cardiovascular	9 (9.0%)
Pulmonary Disease	0 (0.0%)
Kidney Disease	5 (5.0%)
Chronic Liver Injury	0 (0.0%)
Immunodeficiency	0 (0.0%)
Pregnancy	7 (7.0%)
Obesity	1 (1.0%)
Malignancy	1 (1.0%)
Secondary Infection	
Yes	49 (49.0%)
Clinical Severity	
Moderate	22 (22.0%)
Severe	3 (3.0%)
Critical	75 (75.0%)
Length of Stay	
≤14 days	77 (77.0%)
>14 days	23 (23.0%)
End of Treatment Status	
Life	35 (35.0%)
Dead	65 (65.0%)

Table 2. Differences in C-reactive Protein Level Based on Clinical Severity of COVID-19 Patients at Dr. M. Djamil Padang

Clinical Severity	Median of C- reactive levels (min-max)	*P*
Moderate	37.50 (4.90 – >160.00)	
Severe	23.00 (4.90 – 126.00)	0.006*[a]
Critical	0.00 (0.20 – >160.00)	

Note: **P*<0.05 is significant; [a]Kruskal-Wallis test

According to Table 3, the levels of C-reactive protein in deceased patients were higher in those with a length of stay of <14 days (97.00 mg/L) than in those with a length of stay >14 days (88.50 mg/L). The analysis revealed that there were significant differences in C-reactive protein levels in deceased patients based on the length of stay of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (*P*=0.42). C-reactive protein levels were lower in living patientswith <14-day stay (55.00 mg/L) than those with >14 days stay (93.00 mg/L). The result indicated significant differences in C-reactive protein levels in surviving patients based on the length of stay of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (*P*=0.031).

Table 3. Differences in C-reactive Protein Levels Based on Length of Stay in COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Stratification	Length of stay	Median of C-reactive levels (min-max)	*P*
Deceased (n=65)	≤14 hari	97.00 (0.20 – >161.00)	0.042[b*]
	>14 hari	88.50 (16.00 – >161.0)	
Alive (n=35)	≤14 hari	55.00 (0.20 – >161.00)	0.031[b*]
	>14 hari	93.00 (7.9 – >132.0)	

Note: **P*<0.05 is significant; [b]Mann-Whitney test

Table 4 shows that deceased patients had higher levels of C-reactive protein (93.00 mg/L) than those who survived (68.00 mg/L). According to the findings of the study, there were significant differences in C-reactive protein levels based on the final status of COVID-19 patients at Dr. M. Djamil General Hospital, Padang (*P*=0.017).

Table 4. Differences in C-reactive Protein Levels Based on Final Hospitalization Status in COVID-19 Patients Treated at Dr. M. Djamil General Hospital, Padang

Final Hospitalization Status	Median of C- reactive levels (min-max)	*P*
Deceased	93.00 (0.20 – >160.00)	0.017*[b]
Survived	68.00 (0.20 – >1600)	

DISCUSSION

According to the findings of this study, the majority of patients (28.0%) were between the age of 50 and 59, and female (51.0%). Most common comorbid diseases included hypertension (46.0%), diabetes (34.0%), cardiovascular disease (9.0%), pregnancy (7.0%), kidney disorders (5.0%), cerebrovascular disease (4.0%), obesity (1.0%), and malignancy (1.0%). Secondary infections were found in less than half of the total subjects (49.0%). The majority of patients (75.0%) had a critical clinical degree and a length of stay of 14 days (77.0%), and more than half of the subjects (65.0%) died.

This study shows that the majority of COVID-19 patients were female. The result is similar to a study conducted by Fortunato et al involving 1,175

patients, revealing the incidence of COVID-19 was higher in women than men. Research on East Asian women suggested higher expression of ACE2 in women, so they are more likely to get COVID-19.[11]

Surendra's study in Jakarta found different results, revealing that the majority of participants were male.[12] According to another theory, women are less susceptible to COVID-19 infection than men. It is linked to innate immunity, steroid hormones, and sex chromosome factors. When compared to men, the immune regulation gene encoded by the X chromosome in women causes a decrease in viral load and inflammation. Women have higher levels of CD4+ T cells and better immune responses. Women have higher TLR7 levels than men, and biallelic expression allows for a better immune response and increased resistance to viral infections. Men are also associated with a bad lifestyle, such as smoking and drinking more liquor than women.[13]

The Fresan study found an association between hypertension and the severity of COVID-19, although not statistically significant. Hypertension was linked to severe COVID-19 (OR=2.42; 95% CI=1.98-2.96), death (OR=2.60; 95% CI=2.11-3.20), and poor outcomes in patients of all ages (OR=2.50; 95% CI=2.49-4.88).[14] The severity of COVID-19 is related to immune system dysregulation in hypertensive patients. Monocytes in hypertensive patients are hyperactive, producing more IL-6 after stimulation with angiotensin II or lipopolysaccharide, and there is an increase in CD8+ T cells that produce TNF. These CD8+ T cells are unable to fight viral infections and produce an excessive amount of cytokine.[15]

Diabetes patients are 3.69 times more likely to die from COVID-19.[16] Diabetes mellitus was associated with an increased risk of developing severe COVID (OR=2.47; 95% CI=1.86-3.27), death (OR=2.11; 95% CI=1.63-2.73), and a fatal outcome in patients of all ages (OR=2.25; 95% CI=1.89-2.69).[17] The role of hyperglycemia, high cellular affinity binding, efficient viral input, decreased viral clearance, impaired T-cell function, hyperinflammation, cytokine storm syndrome, and the presence of cardiovascular disease are all potential mechanisms by which diabetic patients are more vulnerable to the risk and severity of COVID-19.[18]

Cardiovascular disease is a common comorbidity in COVID-19 patients. A meta-analysis of 8 studies from China on 46,248 COVID-19 patients suggested that the most common co-morbidities included hypertension, DM and cardiovascular disease. The explanation is common cardiovascular disease in elderly patients, as well as functional immune system disorders, make them susceptible to COVID-19 infection.[19]

Pregnant women experience milder COVID-19 symptoms than the general population, but the overall pattern is similar. Pregnant women with COVID-19 may require more ICU admissions and invasive ventilation than non-pregnant women. Mothers with pre-existing comorbidities, as well as those who are obese and of advanced maternal age, should be considered at high risk for COVID-19 infection.[20]

The prevalence of kidney disease in COVID-19 patients is up to 3%, with a mortality rate of around 9% and a cure rate of up to 2%. Kidney disease is linked to an increased risk of pneumonia, as well as an increase in mortality from infection in patients nearing the end of their lives. ACE2 expression in the kidney rises with chronic kidney disease but is unrelated to susceptibility to SARS-CoV-2 infection in other organs, such as the heart. In SARS-CoV-2 infection, the kidney disease underlying COVID-19 is prone to hyperinflammation and a cytokine storm, resulting in severe symptoms. IL-6, CRP, oxidative stress, and metabolic disorders are all factors that contribute to inflammation.[21]

Cancer patients are at a high risk of contracting COVID-19 due to their immunocompromised state and the cancer therapy they receive. The cytokine storm that occurs in cancer patients has a poor outcome with COVID-19 and can progress to ARDS and multiple organ failure. The interaction between SARS-CoV-2 and cancer suggests that patients with cancer are more likely to be infected by SARS-CoV-2, resulting in severe COVID-19 infections and death.[22]

Obesity has an indirect effect on increasing the expression of ACE2, which originates in adipose tissue as cells expressing ACE2. Abnormal cytokine and complement production, results in decreased activity of anti-inflammatory processes Obesity is also associated with an increased risk of blood clots and prolonged viral shedding, both of which contribute to increased mortality in COVID-19.[23]

Secondary bacterial infection is one of the major complications that contribute to the high mortality rate in hospitalized COVID-19 patients. Secondary bacterial infections were found in 19.7% of COVID-19 patients treated in the ICU. The incidence of secondary bacterial infection was found to be higher than previously reported data.[24] Study Secondary bacterial infection was reported to occur in 6.3% of patients by Li et al, and 15% of patients in Zhou et al study had a secondary bacterial infection.[25,26]

In this study, C-reactive protein levels were higher in patients with a clinically critical grade (89.00 mg/L) compared to moderate (37.50 mg/L) and severe (23.00 mg/L). According to the findings, there are significant differences in C-reactive protein levels based on the clinical degree of COVID-19 patients being treated at Dr. M. Djamil Padang. Age ≥70, male, comorbid diabetes mellitus, and pregnancy were the confounding variables for the differences in C-reactive protein levels with the clinical degree of the patients.

According to Luo et al retrospective study, the majority of patients with severe clinical conditions had much higher levels of C-reactive protein than those with mild-moderate clinical conditions (100 vs. 9.65 mg/L).[27] According to Velavan and Meyer's research, patients with high C-reactive protein levels had a worse CT scan than those with mild-moderate clinical manifestations.[28]

According to Acar et al. in Turkey, inflammatory parameters such as C-reactive protein are related to disease severity and can be used as a potentially important risk factor for disease progression (COVID-19.[29] According to Danwang et al, C-reactive protein levels increased in severe COVID- 19 cases in a meta-analysis.[30]

C-reactive protein is a sensitive indicator of tissue injury. During acute inflammation, serum C-reactive protein levels rise. By combining with C-polysaccharide in the bacterial cell wall, C-reactive protein can recognize various pathogens and injured or necrotic cell components. C-reactive protein forms complexes with C-polysaccharides and phospholipids and can activate the complement system to remove pathogens and necrotic cells. Through specific C-reactive protein receptors, C-reactive protein can increase phagocytosis and kill a variety of pathogenic microorganisms.[31]

SARS-CoV-2 infection can result in a cytokine storm, which is associated with high mortality in COVID-19. Cytokines (like IL-6 and TNF-) stimulate hepatocytes to produce C-reactive protein. C-reactive protein is a strong biomarker associated with the development of COVID-19 that rises significantly during the early stages of inflammation and before CT scanning reveals critical findings. A multicenter retrospective study found higher levels of C-reactive protein in thrombotic complications following COVID-19 infection. Obesity and the metabolic syndrome in COVID-19 are linked to chronic systemic inflammatory diseases such as atherosclerosis and hypertension, which have an impact on COVID-19 outcomes. C-reactive protein plays an important role in the inflammatory response and can be used to determine the severity of COVID-19.[31]

The inflammatory process is thought to be related to aging. Several studies have found that in the absence of acute infection, the levels of several cytokines, particularly IL-6, TNF-alpha, and C-reactive protein, rise with age. Other research has linked higher hs-CRP levels to aging. Tang et al. discovered that males had higher hs-CRP levels than females.[32]

C-reactive protein recognizes and binds to specific polysaccharides in the bacterial wall, causing further activation of the complement pathway and pathogen opsonization. C-reactive protein is involved in both proliferative and apoptotic processes via Fc receptor activation and the production of proinflammatory and proapoptotic cytokines. C-reactive protein is not only an indicator of

inflammation, but its level has been linked to type 2 diabetes. The mechanism of the relationship between C-reactive protein and type 2 diabetes is still unclear. Other factors that contribute include oxidative stress and genetic factors such as a family history of type 2 diabetes.[33]

Elevated C-reactive protein is a normal part of pregnancy and is linked to pregnancy complications. The study by Mei et al. compared a sample of women with elevated C-reactive protein (>5 mg/l) to those without elevated CRP (5 mg/l) at 28–32 weeks' gestation to see if there was a difference in stillbirth and premature birth. After 32 weeks, none of the pregnant women who delivered the fetus died. In contrast to previous research that found an increased prevalence of preterm birth in women with high C-reactive protein levels.[34]

C-reactive protein levels were higher in patients with a length of stay of more than 14 days (89.00 mg/L) than in those with a length of stay of 14 days (84.00 mg/L). The analysis revealed that there was no significant difference in C-reactive protein levels in COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. This is presumably because C-reactive protein levels in living and deceased patients were not separated, resulting in inconsistent results. The stratification test was then performed. Stratification results revealed that in patients who died, patients with a length of stay of 14 days (97.00 mg/L) had higher C-reactive protein levels than those with a length of stay of >14 days (88.50 mg/L). The analysis revealed that there were significant differences in C-reactive protein levels in COVID-19 patients who died based on the length of stay at Dr. M. Djamil General Hospital, Padang.

With a length of stay of 14 days, patients who are alive have lower C-reactive protein levels (55.00 mg/L) than patients who are dead (93.00 mg/L). The analysis revealed that C-reactive protein levels differed depending on the length of stay in COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. Variables in COVID-19 patients' length of stay were found to be confounded by differences in C-reactive protein levels.

The findings of this study are consistent with the findings of Lentner et al, who found that the first examination of C-reactive protein was a significant predictor (*P*=0.001) and was related to patient length of stay as well as age (*P*=0.002). LoS was also affected by the number of comorbidities (*P*=0.07). The length of stay (LoS) increased by 0.003 days for every unit increase in C-reactive protein, according to this study. LoS increased by 0.16 days for every 50-unit increase in C-reactive protein (95% CI=0.10–0.21), and by 0.31 days for every 100-unit increase (95% CI=0.20–0.42).[35]

C-reactive protein levels were higher in patients who died (93.00 mg/L) than in those who survived (68.00 mg/L). The findings of this study revealed significant differences in C-reactive protein levels based on the final hospitalization status of COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. The patient's age at the end of treatment was a variable confounder of the difference in C-reactive protein levels.

According to the findings of Devran et al study, C-reactive protein levels can be used to predict mortality in patients with respiratory failure due to sepsis who were treated with a sepsis protocol based on the initial APACHE II score and the SOFA score on the first and third days in the ICU.[36] The Villoteau study found that higher baseline C-reactive protein levels in COVID-19 patients were associated with higher 14-day mortality in COVID-19 geriatric patients.[37]

In 321 adult COVID-19 patients, Bannaga et al found that higher C-reactive protein levels and lower albumin levels on admission to the intensive care unit were associated with higher mortality.[38] In Valerio et al study of 577 middle-aged adults hospitalized with COVID-19, patients who died had higher levels of C-reactive protein than those who survived.[39]

It is unclear why C-reactive protein is associated with decreased survival in older COVID-19 patients.[37] Some of the potential causes include:

a. C-reactive protein levels are reported to be positively correlated with lung lesions in the early stages of COVID-19 and can be used as a biomarker of disease severity.[8]

b. Hepatocytes produce C-reactive protein, which is linked to IL-6, which is involved in the cytokine storm. This will result in increased VEGF secretion and decreased E-cadherin expression, both of which contribute to increased vessel permeability, arterial hypotension, organ failure, and ARDS.[40]
c. Inflammatory conditions associated with elevated C-reactive protein levels can cause prothrombin to be released, increasing the risk of stroke or venous thromboembolic events.[41]
d. As a compensatory response in respiratory distress, elevated C-reactive protein induces hypercatabolism associated with respiratory muscle protein consumption.
e. C-reactive protein levels in older people can be used to assess pre-COVID-19 health status and to describe chronic disease, both of which are major risk factors for severe COVID-19.[37]

LIMITATION

This study has limitations, such as the use of a retrospective cohort design based on data from patient medical records and the uneven distribution of patients in various clinical degrees. This study was also unable to assess C-reactive protein levels at all COVID-19 clinical levels.

CONCLUSION

The majority of COVID-19 patients in this study were women between the ages of 50-59 years, with the majority having hypertension and critical clinical severity. There are significant differences in levels of C-reactive protein based on the degree of clinical COVID-19 patients with confounder variable age ≥70 years, males with comorbid diabetes mellitus and pregnancy. There are significant differences in levels of C-reactive protein based on the duration of treatment of COVID-19 patients. There are significant differences in C-reactive protein levels based on the final hospitalization status of COVID-19 patients with confounder variable age ≥70 years.

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CONFLICT OF INTEREST

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Systematic Review

Education on Inhaler Technique by Pharmacists To Improve The Quality of Life of COPD Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: This systematic review aimed to analyze the importance of education on using inhalers by pharmacists in improving quality of life, correct inhaler use steps, and medication adherence in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods: The databases used to search for articles in this systematic review include Scopus, ScienceDirect, and Pubmed. The papers submitted were published between 2009 and 2022, with the most recent search being conducted in December 2022. This review included a randomized controlled trial evaluating education on inhaler use techniques by pharmacists to improve COPD patients' quality of life in inpatient and outpatient settings. This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) writing guidelines.

Results: This systematic review used six articles from five different countries. The articles involved share similar characteristics so that analysis can be carried out. The total number of research subjects included was 913 subjects. Most studies show an increase in the quality of life among COPD patients who are given education on how to use inhalers by pharmacists using print or digital media. Measurements using the St. George's Respiratory Questionnaire (SGRQ) showed a decrease in scores at the 6-month and 12-month periods (-0.75 [95% CI = (-1.46) - (-.005)]. Furthermore, two articles reported that education on the technique of using inhalers by pharmacists can also increase the accuracy of using inhalers, and three articles reported increasing medication adherence.

Conclusion: Interventions such as education on using inhalers by pharmacists in inpatient and outpatient settings can improve the quality of life of COPD patients, the accuracy of the steps in using inhalers, and medication adherence.

Keywords: COPD, hospital pharmacist, inhaler technique education

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (shortness of breath, coughing, sputum production) caused by abnormalities of the respiratory tract (bronchitis/bronchiolitis) and alveoli (emphysema), resulting in persistent, progressive, and airway obstruction.[1] COPD is a leading cause of death and disability worldwide. According to The Global Burden of Disease Study 2019, COPD is the sixth leading cause of death, up from 11th in the previous ranking.[2] COPD prevalence reached 212.3 million in 2019, with 3.3 million deaths and 74.4 disability-adjusted life years (DALYs).[3] The rise in COPD cases worldwide can be attributed to various risk factors, including smoking status, cigarette smoke exposure, occupational exposure to particulates, gases, and smoke, household air pollution from solid fuels, ambient ozone pollution, and low and high temperatures.[4]

Chronic obstructive pulmonary disease prevalence is expected to rise in the coming years, and the World Health Organization predicts that COPD will be the third leading cause of death in the world by 2030.[5,6] Based on this, effective COPD management in the form of lifestyle changes and long-term commitment to treatment in patients already receiving treatment is required to prevent increased morbidity.[5,7]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), inhalation therapy

is the primary treatment recommended to improve symptoms in COPD. Several studies have found that poor adherence to inhaler use is caused by inappropriate use of inhalers and poor inhalation techniques. Non-compliance with inhalation therapy results in decreased lung function, more exacerbations, and an increased risk of hospitalization.[8,9]

According to one study, data on non-adherence to therapy in COPD patients reached 79.4% of 504 patients, and only 6.3% of 765 patients can use inhalers properly.[10,11] Therefore, education in inhaler use plays a vital role in managing COPD patients. It should be emphasized that patient education about inhaler use is carried out when prescribing inhaler devices, and it is recommended that inhaler use be assessed at each visit. Repeated education and assessments are required to maintain proper inhalation technique and patient compliance regularly.[9,12]

Only one systematic review with a randomized controlled trial study reported that the pharmacist's role in the hospital has contributed to various aspects of COPD management, both inpatient and outpatient.[13] Therefore, this systematic review aimed to evaluate specifically the impact of providing education on the technique of using inhalers by hospital pharmacists in improving the quality of life of inpatient and outpatient COPD patients. The purpose of selecting inpatients and outpatients is to assist patients in enhancing treatment safety, patient outcomes, and drug quality over time and to prevent readmissions in inpatient settings.[14,15]

METHODS

Search databases such as Pubmed, ScienceDirect, and Scopus were used to search literature. The articles in this search were those published in 2009-2022, with the last examination in December 2022. The combination of keywords used in the investigation in this article were Pharmacy, COPD, Inhaler, Hospital, Outpatient, and Quality of life.

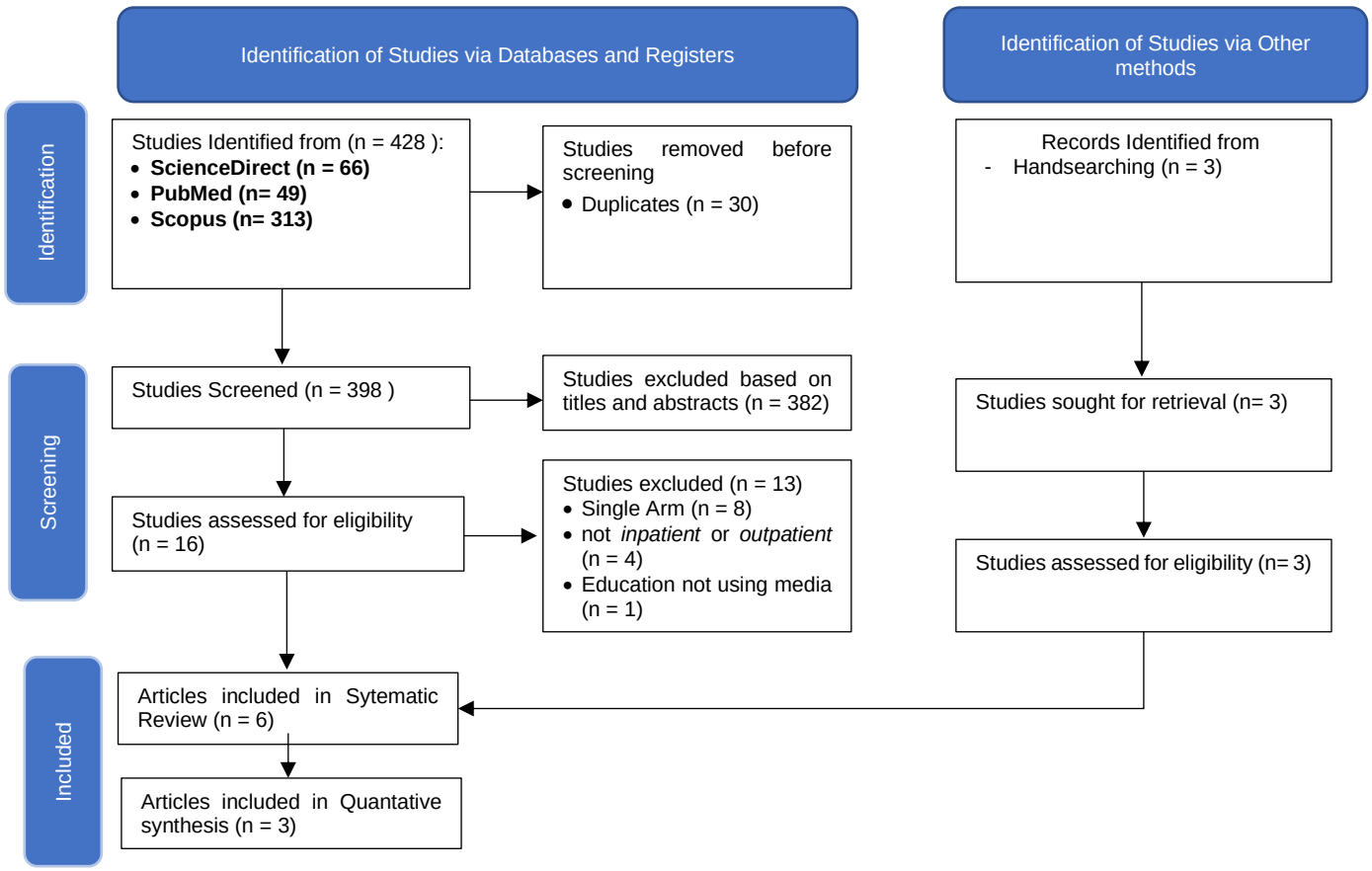

Figure 1. PRISMA Flowchart

The inclusion criteria used in this review were the PICO criteria as follows:

a. Participation/Population: COPD inpatients and outpatients
b. Intervention/Exposure: Pharmacists provide verbal or face-to-face instruction on the proper use of inhalers, supplemented by leaflets, videos, and other media.
c. Comparator/Control: Education on inhaler use techniques by pharmacists only verbal or face-to-face.
d. Outcome: The primary outcome is assessing the quality of life of COPD patients using the COPD Assessment Test (CAT), St. George Respiratory Question (SGRQ), and Other Instruments of Quality of Life. The secondary outcomes in this systematic review are correct inhaler technique and medication adherence.

The exclusion criteria set in this review were non-English speaking articles, non-open access articles, non-original research articles, and non-randomized controlled trial (RCT) articles.

Two reviewers (SA and VP) extracted all research articles using Microsoft Excel and Mendeley. Differences in data extraction were resolved by the third reviewer (RS). The reviewers screened the articles that met the inclusion and exclusion criteria set by agreement with a Kappa value of 0.86. The data extraction process was then depicted in the flowchart of The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), as listed in Figure 1.

To reduce the risk of bias, the stages of article screening are carried out by two independent reviewers using The Medical Education Research Study Quality Instrument (MERSQI) Score.[16] The Medical Education Research Study Quality Instrument (MERSQI) can be used to assess the quality of experimental studies. It consists of ten items with six domains of study quality. The domain of study quality encompasses study design, sampling, data type (subjective or objective), validity, data analysis, and results. The maximum score for each domain is 3, with a top score of 18, and the possible scores range from 5 to 18.[17]

The studies included in this review were summarized using the narrative description method. This review focused on improving the quality of life in COPD patients who receive education on using inhalers via media such as leaflets or videos. The quality of life assessment instruments used were the St-George Respiratory Questionnaire (SGRQ) and the COPD Assessment Test (CAT). In the CAT and SGRQ assessment instruments, COPD patients are said to have a good quality of life if their CAT and SGRQ scores are low, with a maximum CAT score limit of 40 points and an SGRQ score limit of 100 points.

We analyzed the RCT data using Review Manager 5.4 (RevMan 5.4.1), which was made available by Cochrane. Analyzed data consists of continuous data measured using Standardized Mean Difference (SMD). Standardized Mean Difference (SMD) was utilized because the included studies collected data at different scales or units. Subsequently, using the random-effects method, observe the effect. Quantitative evaluation of heterogeneity using Cochrane I^2 statistics. A random effects model is applied if I^2 is greater than 50 percent, indicating statistically significant heterogeneity; otherwise, the effects model is maintained. We performed subgroup analysis in high heterogeneity (I^2 >50%) to identify good heterogeneity causes.

RESULTS

Based on article searches through database searches, 428 articles were obtained, and three were obtained through other search methods. The search for these articles yielded six articles that met the PICO criteria established in this review. The articles included in this study had good agreement reached by three reviewers (SA, VP, RS) with a Kappa value of 0.86. The study quality was examined using The Medical Education Research Study Quality Instrument (MERSQI) Score and is presented in Table 1. Based on the assessment of study quality using the MERSQI score, six studies included in this review received an average score of 14. This score falls within the MERSQI's potential range of 5–18.[17]

Table 1. Results of The MERSQI Score

Domain	MERSQI Item	Score	Wang et al, 2020	Suhaj et al, 2015	Xin et al, 2016	Khdour et al, 2009	Jarah et al, 2011	Kebede et al, 2022
Study Design	Single-group cross-sectional or single-group post-test only	1						
	Single group pre-test & post-test	1.5						
	Non Randomized, two groups	2						
	Randomized Controlled Trial	3	✓	✓	✓	✓	✓	✓
Sampling	Institutions studied :							
	1	0.5	✓	✓	✓	✓	✓	✓
	2	1						
	3	1.5						
	Respons rate, %							
	Not applicable	-						
	<50 or not reported	0.5						
	50-74	1						
	≥75	1.5	✓	✓	✓	✓	✓	✓
Type of Data	Assessment by participants	1	✓	✓	✓	✓	✓	✓
	Objective measurement	3						
Validity of Evaluation Instrument	Internal structure							
	Not applicable	-						
	Not reported	0						
	Reported	1	✓	✓	✓	✓	✓	✓
	Content							
	Not applicable	-						
	Not reported	0						
	Reported	1	✓	✓	✓	✓	✓	✓
	Relationships to other variables							
	Not applicable	-						
	Not reported	0	✓	✓	✓	✓	✓	✓
	Reported	1						
Data Analysis	Appropriateness of analysis							
	Inappropriate for study design or type of data	0						
	Appropriate for study design or type of data	1	✓	✓	✓	✓	✓	✓
	Complexity of analysis							
	Descriptive analysis only	1						
	Beyond Descriptive analysis	2	✓	✓	✓	✓	✓	✓
Outcome	Satisfaction, attitudes, perceptions, opinions, general facts	1						
	Knowledge, skills	1.5						
	Behaviors	2						
	Patient/health care outcome	3	✓	✓	✓	✓	✓	✓
	Total Possible score	18	14	14	14	14	14	14

The studies in this review were conducted in various countries, including India, Ireland, Jordan, Norway, and China. All of the studies used a randomized study design with two groups. All subjects in the study had been diagnosed with COPD using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and were over 45 years old. The COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire (SGRQ) were used in all studies to assess COPD patients' quality of life.

Table 2 displays data from the articles used in this review on the characteristics of COPD patients. According to the table, several articles are missing economic conditions, education level, type/level of work, and smoking status.

Table 2. Characteristics of COPD Patients

Authors	Location	Setting	COPD risk factors (excluding age)			
			Education	Type/Level of Work	Economic Conditions	Smoking Status
Khdour et al, 2009[18]	Northern Ireland	*Outpatient*	Moderate (71.70%)	Lower (63.55%)	n/a	Ex-Smokers (65.30%)
Jarab et al, 2012[19]	Jordan	*Outpatient*	Lower (90.20%)	Lower (60.15%)	n/a	Current Smokers (56.55%)
Suhaj et al, 2015[20]	India	*Outpatient*	n/a	n/a	Lower (36.60%)	Current Smokers (55.35%)
Xin et al, 2016[21]	China	*Outpatient*	Lower (70.45%)	n/a	n/a	Current Smokers (74.40%)
Wang et al, 2020[22]	China	*Outpatient*	Lower (47.00%)	n/a	n/a	n/a
Kebede et al, 2022[23]	Norway	*Inpatient*	n/a	n/a	n/a	n/a

Table 3. The Outcome of Quality of Life Using St. George Respiratory Questionnaire (SGRQ)

Authors	Type of Intervention	Time	Control Group*	Intervention Group*	*P*
Khdour et al, 2009[18]	Booklet regarding the use of inhalers and COPD management	Baseline	64.20	63.60	0.690
		Six months	64.20	59.20	0.040
		12 months	65.30	61.80	0.170
Jarab et al, 2012[19]	Booklets regarding the use of inhalers and knowledge about COPD	Baseline	44.80	45.20	0.760
		Six months	42.70	42.30	0.510
Suhaj et al, 2015[20]	Patient Information Leaflets (PILs)	Baseline	50.60	50.90	0.949
		Six months	49.20	47.20	0.618
		12 months	52.40	42.70	0.024
Xin et al, 2016[21]	Inhaler use educational leaflet Face to face COPD related education	Baseline	68.40	68.50	0.913
		Six months	68.30	61.70	0.001
		12 months	67.80	61.62	0.001
		18 months	68.50	61.31	0.001
		24 months	68.50	60.40	0.001

Note: *SGRQ Total Score

Table 4. The Outcome of Quality of Life Using COPD Assessment Test (CAT)

Authors	Type of Intervention	Control Group*			Intervention Group*		
		Pre	Post	*P*	Pre	Post	*P*
Wang et al, 2020[22]	Brochures regarding COPD and how to use inhalers Video of inhaler use is sent to the patient's cell phone	19.39	18.44	0.461	19.81	15.67	0.021
Kebede et al, 2022[23]	Information sheet regarding inhalers, such as effects (reliever/controller), onset, side effects that often arise, and techniques for using inhalers	24.00	24.00	>0.05	29.00	25.50	0.290

Note:*CAT Total Score

Two studies measured the quality of life instrument with the CAT and four studies with the SGRQ. Research conducted by Jarab et al, Khdour et al, Suhaj et al, and Xin et al showed improved quality of life based on an assessment using the SGRQ instrument.[18–21] However, the increase in quality of life in the study conducted by Jarab et al was not significant.[19]

Other studies conducted by Wang et al and Kebede et al reported that providing education on the use of inhalers using videos or information sheets can improve the quality of life in COPD patients as assessed by the CAT instrument.[22,23] Kebede et al reported a decrease in the median CAT value of the intervention group between baseline and two months following discharge by 3.5 points. However, this result was not statistically significant compared to the control group two months after discharge (P>0.05).[23] Meanwhile, Wang et al reported a substantial decrease in the average CAT score in the intervention group of 4.15 points (P<0.05) compared to the control group, which showed no significant differences between the pre-and post-intervention periods (P>0.05).[22]

The subgroup meta-analysis was conducted between different measurement instruments and assessment periods. Due to the limited availability of studies analyzed using the CAT instrument, subgroup analysis was exclusively conducted utilizing the SGRQ instrument. According to the results of the analysis, administering the intervention can substantially reduce the SGRQ score during the 6th and 12th month assessment periods (-0.75 [95%

CI (-1.46–(-.005)]. The effect of subgroup analysis on I^2 scores was insignificant (Figure 2).

In this systematic review, two studies reported data related to the accuracy of inhaler use technique accuracy in COPD patients. Wang et al found a statistically significant difference between the control and intervention groups after administering the intervention (P<0.05).[22] In contrast, Kebede et al found no statistically significant differences between the intervention and control groups (P>0.05) when the intervention was administered to both groups.[23]

A total of three studies reported medication adherence data on COPD patients. Two methods are used to measure medication adherence, including the medication refill adherence method, which was used in one study, and the Morisky Scale method, which has been used in two studies.[18,19,21] Khdour et al and Jarab et al reported that there was a statistically significant difference (P<0.05) in measuring medication adherence using the Mosrisky scale method after intervention in the control and test groups.[18,19] Xin et al showed similar results using the medication refill adherence method.[21]

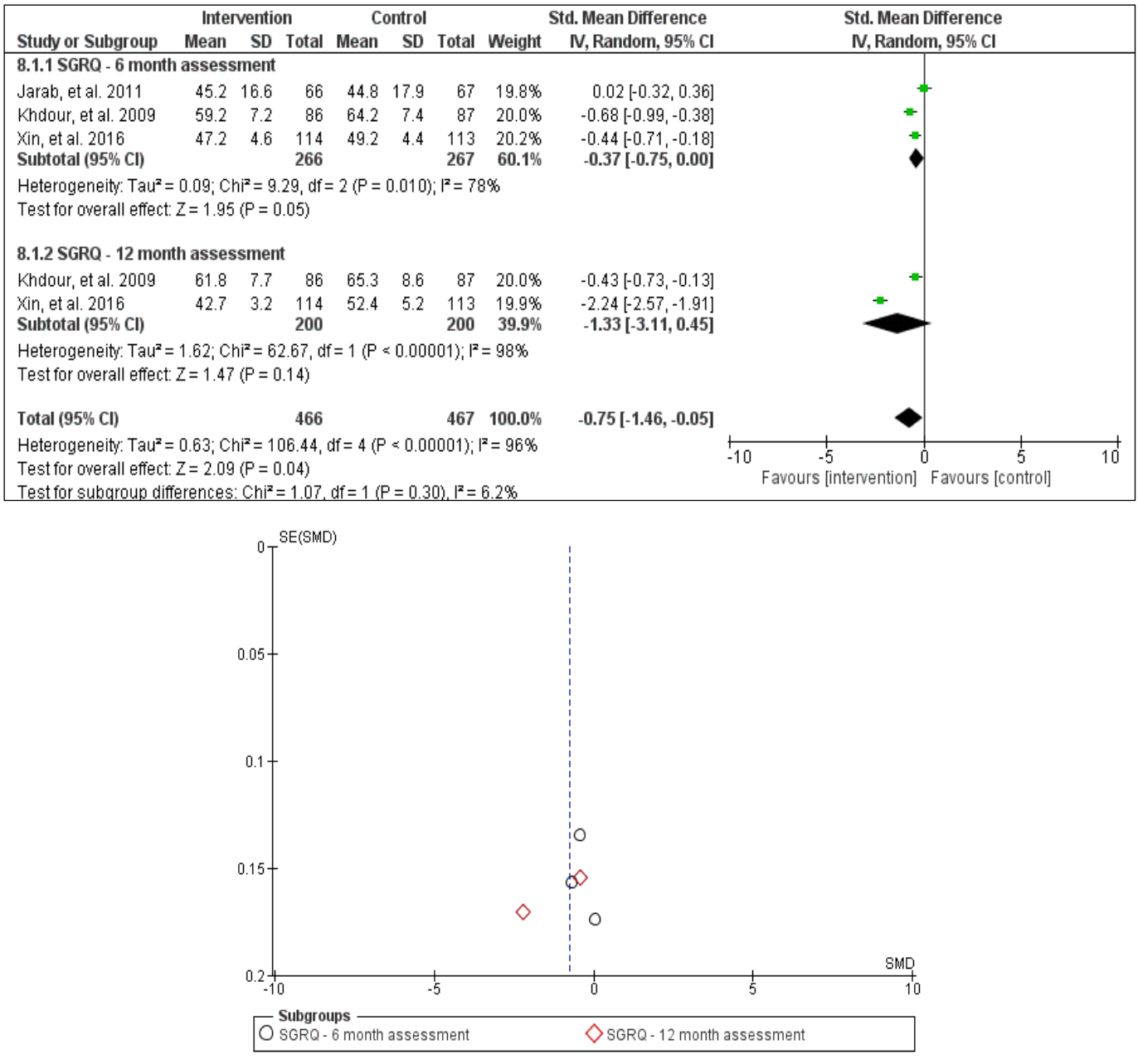

Figure 2. Forest Plot and Funnel Plot of Quality of Life by SGRQ instrument

DISCUSSION

Six articles met the criteria for inclusion and exclusion based on the systematic review's inclusion and exclusion rules. The studies in this systematic review share similar results, even though they were conducted at six locations. This is by data from The Global Burden of Disease Study 2019, which states that the risk factors for COPD include smoking, exposure to cigarette smoke, household air pollution from solid fuels, ambient particulate matter, ozone, and occupational particles.[4]

Four studies used the SGRQ instrument to measure the quality of life of COPD patients, and 2 studies used the CAT instrument to evaluate COPD patients' quality of life.[18–23] GOLD recommends both of these instruments in measuring the quality of life of COPD patients. Compared to the CAT, which only has 8 question items, the SGRQ instrument has 50 more complex questions. Although the question items from the two instruments differ, they have a strong correlation (r=0.73–0.80).[24,25] One study using the CAT instrument showed a non-significant improvement in QoL at the 2-month follow-up period (P>0.01).[23]

A total of 3 studies measuring the quality of life using the SGRQ instrument showed insignificant results at a specific follow-up period.[18,19,21] The occurrence of a negligible improvement in quality of life could be caused by several factors, including small sample size, short follow-up duration, repeated education during the follow-up period, whether or not additional educational materials were provided in addition to inhaler use techniques, the level of education, and socioeconomic conditions.[18,19,26,27]

In the original research reported in this systematic review, three articles reported outcomes regarding medication *adherence.*[18,19,21] Medication Adherence is one of the critical factors in suppressing COPD progression, which can also increase mortality and readmission.[28] Of the three articles, two used the Morisky Scale method, while another used medication refill adherence. These three studies showed that pharmacist interventions could significantly increase adherence in COPD patients (P<0.05). This shows similar results to those of Nguyen et al that interventions provided by pharmacists can improve compliance over time.[29]

Adherence in COPD patients can be influenced by three main factors, including medication, unintentional, and intentional. Drug factors are those that are directly related to the drug, such as drug side effects and the ease of inhalers, as well as the correct inhalation technique, which can be difficult for patients to acquire, and other factors that are essential for achieving the optimal inhalation therapy.[30] Intentional factors are non-adherence caused by patient intent, including patient perceptions that treatment is unnecessary, resistance to treatment, inappropriate expectations, focus on side effects, cultural or religious issues, and costs. Unintentional factors include unintentional patient misperceptions of therapy, such as costs, forgetting to take medications, and misinterpreting inhaler usage instructions inhaler.[31]

In this systematic review, two studies reported outcomes using the correct technique of inhalers. A study conducted by Wang et al showed an improvement in the accuracy of using inhalers in the intervention group after monthly education was carried out during the follow-up period (P<0.01).[22] Meanwhile, a study conducted by Kebede et al showed no significant difference between the control and intervention groups in terms of increasing the accuracy of the inhaler technique (P>0.05).[23]

Based on the two articles, there is a finding that repeating education at each visit can improve patients' understanding of how to use inhalers correctly. The two articles provide the same results regarding the steps of inhaler use, which often lead to inhaler misuse. The steps that often cause mistakes are standing straight before using the inhaler, breathing before using the inhaler, and holding breath after inhaling the inhaler. These errors affect effective drug inhalation and increase the risk of hospitalization or emergency room visits.[32]

The final results of our systematic review highlight the significance of hospital pharmacists in administering COPD treatment, with potential implications for medication adherence, inhaler

accuracy, and COPD patients' quality of life. This systematic review updates the previous evaluation by adding a 2022 RCT study. We compare the provision of education by pharmacists in inpatient and outpatient settings to improve quality of life, appropriateness of inhaler use, and treatment adherence in COPD patients. According to our most recent study, there was no discernible difference between the control and the intervention groups regarding pharmacist education to reduce readmissions over the 12-month follow-up period (P=0.30).[23]

This is due to an imbalance in patient characteristics between the control and intervention groups. The intervention group had more study subjects who had readmissions in the last year, a large number of inhalers used, high CAT scores, and many had comorbidities compared to the control group. Some patients had a comorbid disease, and the cause of readmission was pneumonia (n=1), non-infectious exacerbation of asthma (n=1), pleural effusion (n=1), scheduled invasive test (n=4), congestive heart failure (n=1), fall (n=1), erysipelas (n=1), chest pain (n=1), and atherosclerosis (n=1).

LIMITATION

The limitations of this systematic review are the limited research on hospital pharmacists or clinical pharmacists regarding education on inhaler use and COPD management in outpatients and inpatients involving two research groups and pre-post intervention assessments. The advantage of this systematic review is that only prospective RCT-based articles are included for analysis.

CONCLUSION

Hospital pharmacists' education on inhaler use can enhance the accuracy of inhaler steps and medication adherence in COPD inpatients and outpatients. Therefore, the quality of life of COPD patients can be improved. Future studies should compare the results of RCTs on inhaler education with clinical outcomes, like testing the lung function of COPD patients in inpatient or outpatient settings.

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CONFLICT OF INTEREST

This review has no conflict of interest.

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Literature Review

Bronchoalveolar Lavage (BAL) in Pulmonary Alveolar Proteinosis and Sarcoidosis

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Abstract

Bronchoalveolar lavage (BAL) is a minimally invasive procedure using flexible fiber optic bronchoscopy guidance that is safe, easily performed, and well tolerated. Bronchoalveolar lavage procedure is important to diagnose or differentially diagnose patients with a clinical appearance and radiological findings that are not specific. Mechanisms related to lung disorders such as inflammation, fibrosis, and abnormal material could be obtained by BAL fluid. Non-infection lung disorders such as pulmonary alveolar proteinosis (PAP) and sarcoidosis may be diagnosed by BAL. BAL in non-infection lung disease has diagnostic and therapeutic functions. As diagnostic function, BAL could be a tool to obtain a lower respiratory tract sample, and lavage from the respiratory track could be a therapeutic function of BAL.

Keywords: bronchoalveolar lavage, pulmonary alveolar proteinosis, sarcoidosis

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INTRODUCTION

Bronchoalveolar lavage (BAL), or bronchoalveolar lavage, was first introduced in clinical practice in 1974 as a diagnostic tool for lung diseases.[1] Since then, the use of BAL with the guidance of flexible fiberoptic bronchoscopy (FOB) has been widely used as a diagnostic tool for various lung diseases, especially interstitial lung diseases (ILD). BAL is performed with the help of FOB to sample the lower airway by rinsing the bronchoalveolar segment.[2] Therefore, the development of BAL is inseparable from the invention of FOB in 1960, which has safety and convenience in the visualization of lesions and bronchial biopsy, elbow, and bronchial rinse for sampling the diagnosis of lung disease.[3]

BAL is a minimally invasive procedure using FOB guidance that is safe, easy to operate, and well tolerated by patients.[4] Samples obtained from BAL are taken from a larger area than transbronchial biopsies so that they can provide additional information to support patient diagnosis and have advantages over histopathology biopsies.[5] BAL samples reflect pathological changes associated with elements of the lung parenchyma and can therefore be used as a diagnostic tool.[6] Pulmonary alveolar proteinosis (PAP) and sarcoidosis are inflammatory disorders of unknown cause that can affect the lungs. The diagnosis of both diseases is difficult; however, by analyzing the specimens from BAL for histopathologic examination, we can improve our ability to diagnose as well as treat both diseases. This review will discuss the use of BAL in non-infectious lung diseases, focusing on PAP and sarcoidosis.

BRONCHOALVEOLAR LAVAGE

BAL is the collection of lower airway samples by the instillation of sterile physiological fluid into the lung subsegment, followed by suction and collection

of the instillation fluid for analysis. BAL is performed using FOB guidance with topical anesthesia to prevent coughing. In addition, BAL can also be performed under general anesthesia and in patients with assisted ventilation via rigid bronchoscopy or endotracheal tube.[5] The total volume of fluid instilled during BAL should be at least 100 mL but not more than 300 mL, divided into three to five aliquots that are withdrawn per instillation. To obtain a good sample, the total volume of recalled fluid should be more than 30% of the total instilled fluid.[7] Through this technique, cells, inhaled particles, infectious organisms, lower airway solutes, and alveolar epithelial cells can be retrieved. Information such as immunology, inflammation, and infectious processes occurring in the alveoli can be found in BAL.[8]

INDICATIONS, CONTRAINDICATIONS AND COMPLICATIONS OF BAL

Airway symptoms, nonspecific radiological findings, and clinical symptoms suggestive of a diagnosis of ILD are indications for BAL.[9] In addition, BAL is also performed in patients with normal thoracic images accompanied by clinical abnormalities and pulmonary function tests suggestive of diffuse lung disease. In patients with unexplained respiratory symptoms, normal BAL findings may rule out the diagnosis of ILD. Clinicians need to perform BAL as additional and confirmatory information in establishing a diagnosis based on the findings of high-resolution computed tomography (HCRT) that cannot establish a diagnosis or when confirming additional information and confirming or ruling out a diagnosis. However, BAL cannot be a single diagnostic tool so it must be combined with clinical findings, laboratory examinations, and HRCT.[5,8]

The absolute contraindications for performing BAL are the same as those for bronchoscopy, such as cardiac arrhythmias and cervical disorders. Relative contraindications for BAL include uncooperative patients, forced expiratory volume in the first second (FEV_1) less than one liter, asthma with moderate airway obstruction, hypercapnia, hypoxemia that cannot be corrected to PaO_2 75 mmHg or O_2 saturation more than 90% with O_2 therapy, cardiac arrhythmia, myocardial infarction in the last 6 weeks, unresolved bleeding, and unstable hemodynamics.[10] In general, BAL is well tolerated by patients. However, some of the complications that occur are similar to those that occur with FOB. A minor complication that can occur after BAL is fever. This complication can be reduced by keeping the volume of BAL instillation less than 150 mL.[5] The fever that occurs after BAL may disappear without treatment within 24 hours. In patients with ILD, less than 5% of patients undergoing BAL experience minor complications such as post bronchoscopy fever, pneumonitis, bleeding, and bronchospasm.[7]

USEFULNESS OF BAL IN NON-INFECTIOUS LUNG DISEASES

The usefulness of BAL in diagnosing non-infectious lung diseases such as ILD is still a challenge, but BAL can be a definitive diagnostic tool if the results obtained are consistent with clinical findings and radiological data. The morphology of BAL fluid provides important information for diagnosing ILD. If the BAL fluid appears very cloudy or milky, light brown or beige in color, and there are white clots deposited at the bottom of the container, the diagnosis is most likely PAP.[2]

Lymphocyte subset analysis of BAL fluid provides important information when cell type analysis shows a lymphocyte cell presentation of ≥15%. An increase in CD4 and a decrease in CD8, along with an increase in the ratio between CD4 and CD8 counts, leads to the diagnosis of sarcoidosis when supported by appropriate clinical appearance and radiological features.[2] In addition to being useful for diagnosis, BAL is also useful as a therapy in PAP by modifying whole lung rinses.[11]

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis is a rare disease characterized by an imbalance in pulmonary surfactant homeostasis and accumulation of lipoprotein material in the alveoli. There are three classifications of PAP: primary PAP (autoimmune

and hereditary), secondary PAP (quantitative and/or qualitative destruction of macrophages in the alveoli) and unqualified PAP (neither of the previous criteria). Factors that play a role in the pathogenesis of PAP, resulting in progressive filling of the alveoli, include lipoproteins and surfactants.[12,13] Surfactant consists of a mixture of 10% protein surfactants (SP) such as SP-A, SP-B, SP-C, and SP-D and 90% lipids, mainly phospholipids secreted by type II pneumocytes.[14]

Surfactant functions to maintain the lung by forming a layer between air and fluid on the surface of the alveoli, reducing pressure, and preventing the alveoli from collapsing. The amount of surfactant is regulated by the balance of secretion and clearance of type II pneumocytes and alveoli macrophages. Granulocyte macrophages-colony stimulating factor (GM-CSF) is known to be key in regulating surfactant catabolism in alveoli macrophages. Research into the occurrence of PAP has been demonstrated in experimental mice that lack the GM-CSF gene. This underlying mechanism leads to impaired surfactant clearance and is classified as primary PAP, while secondary PAP is associated with an underlying disease that causes disruption of alveolar macrophage function.[14,15]

BAL fluid analysis can be used to confirm PAP. Macroscopically, a milky white fluid is seen due to the accumulation of surfactant derivatives such as phospholipid components and proteins in the alveoli.[8] Examination of BAL fluid using a microscope shows that the cell pattern shows an increase in lymphocytes, neutrophils, and eosinophils.[16] The macrophage picture is fatty, and there is sediment so that the appearance looks cloudy with May-Grunwald-Giemsa (MGG) staining. The cytology of BAL fluid obtained in PAP patients is positive for Periodic Acid-Schiff (PAS) and oil-red-O staining.[14] Ultrastructural examination using electron microscopy of BAL fluid found type II pneumocyte cells containing a circular layer structure, some containing osmophilic dense nuclei, and surrounded by protein debris.[12,17] The discovery of GM-CSF neutralizing antibodies in serum and BAL fluid indicates this disease is an autoimmune process.[18]

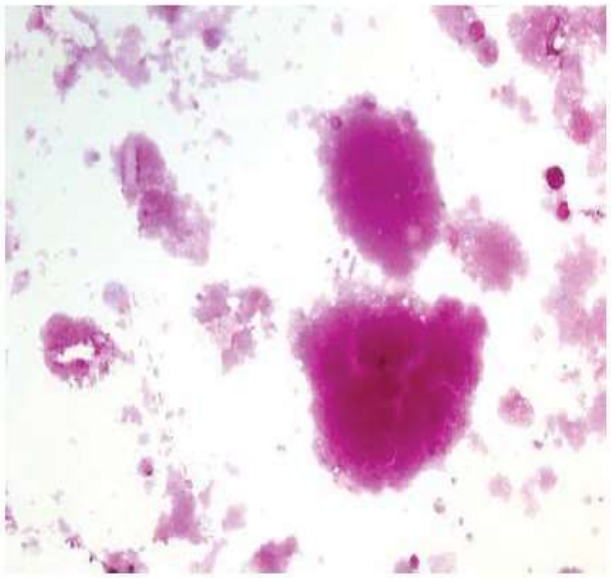

Figure 1. Positive PAS staining in BAL fluid cytology of PAP patients.[14]

Krebs Von De Lungen-6 (KL-6), a high molecular weight glycoprotein commonly used as a tumor marker and increased in lung cancer patients, especially adenocarcinoma, is also known as a marker of diffuse ILD. A study using immunohistochemical examination of BAL fluid obtained an increase in KL-6 values higher than serum KL-6 values in PAP patients. This increase in KL-6 value in PAP patients is higher than the KL-6 value in other ILDs, so a sharp increase in KL-6 value indicates a diagnosis of PAP.[19]

In addition to its role in PAP diagnostics, BAL is also useful in PAP management by performing whole lung lavage (WLL). The procedure is performed under general anesthesia using a double-bore endotracheal tube to ventilate one lung and perform lavage in the other lung. Rinses are performed using warm saline fluid totaling 5-40 L in one lung to remove lung surfactant.[13,20]

Whole lung rinses in PAP are generally performed in stages in each lung with the more severely affected lung being performed first based on radiologic features. Subsequent lavage of the second lung is safer as the disease improves after the first whole-lung lavage therapy.[13] Repeated partial lung lavage can reduce KL-6 values in BAL fluid and serum, followed by improvement in lung function and radiologic features.[19]

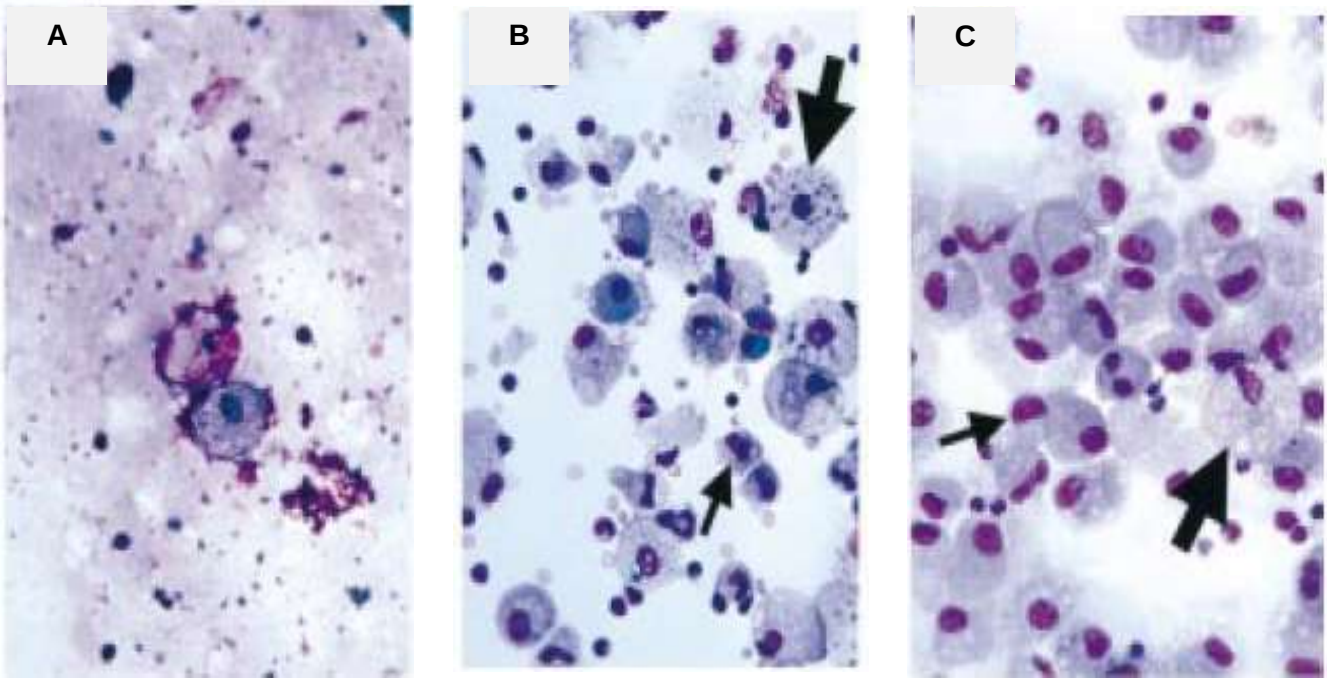

Figure 2. BAL fluid cytology before treatment (figure A), after six weeks treatment (figure B) and after 12 weeks treatment (figure C). Small arrows are small monocyte-like cells and large arrows are fat-containing macrophages.[21]

BAL measures can be used for follow-up PAP therapy.[22] In PAP patients who received GM-CSF therapy, BAL fluid images before therapy showed fatty macrophages with extracellular protein material that gradually improved. After six weeks of GM-CSF therapy, extracellular amorphous material and cellular debris were no longer found. The macrophage population consisted of small monocyte-like cells without intracellular protein material (33%), large fatty macrophages with intracellular protein material (62%), and few large macrophages (3%). At the evaluation of 12 weeks of GM-CSF therapy, the macrophage population changed, consisting of macrophages containing fatty proteins (90%), only 10% of small monocyte-like macrophages and no large macrophage cells. BAL fluid anti-GM-CSF antibody titers decreased from 4.4 µ/mL before therapy to 0.14 µ/mL after six weeks of therapy and 0.13 µ/mL after 12 weeks of therapy.[21]

Sarcoidosis

Sarcoidosis is an idiopathic granulomatous systematic disease that affects the lungs and often involves multiple organs.[23] Symptoms often include shortness of breath, coughing, and fatigue. Spontaneous improvement occurs in many patients, however, some patients develop chronic disease. The etiology of sarcoidosis is still unknown, but the presence of Th1 (T helper 1) CD4+ and macrophages in BAL fluid and blood is a factor in granuloma formation in the lung, which is believed to be an autoimmune disease-causing antigen. The diagnosis of sarcoidosis is established by clinical symptoms and/or radiologic features as well as histologic findings of granulomatous, non-caseous inflammation by excluding other causes of local reactions. Granuloma formation is induced by antigen in the form of antigen-presenting cells (APC) to CD4+ naive T cells (Th0). Th0 cells will then be activated and differentiate into Th1 due to the influence of dendritic cells.[24] Suspicion of sarcoidosis is made if there is an increase in lymphocytes with negative mycobacterium culture from BAL fluid.[23]

At the time of diagnosis, 90% of patients with sarcoidosis have elevated lymphocytes in BAL fluid which is not affected by sarcoidosis staging. Patients with active sarcoidosis tend to have higher lymphocytes counts than those with inactive sarcoidosis, although 10-15% of patients have normal lymphocyte counts. Neutrophil and mast cells are increased in advanced sarcoidosis. In addition, BAL also provides information through cell fraction analysis with T lymphocyte subset analysis.[25]

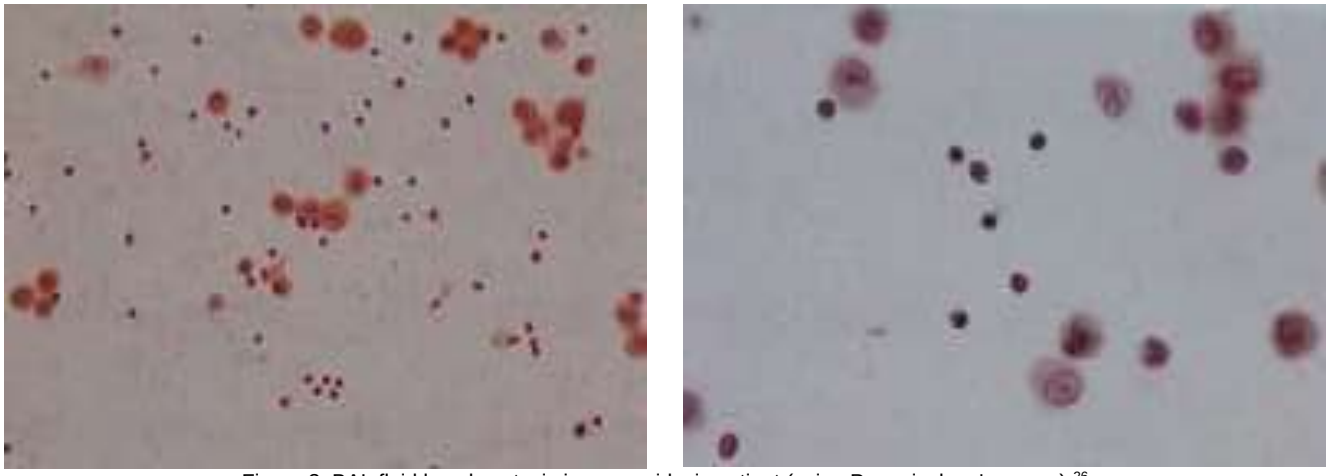

Figure 3. BAL fluid lymphocytosis in a sarcoidosis patient (using Papanicolaou's smear).[26]

Table 2. Characteristics of BAL fluid cell type counts of sarcoidosis patients and healthy individuals.[27]

Cells	Healthy	Without symptom	With symptoms	Treated
Total cells ($x10^6$/mL)	254±247	334±273	411±322	292±166
Macrophages, %	79±8	56.4±17	49.3±20	55.5±15
Lymphocyte, %	15.7±7	39±17	45±19	39±15
Neutrophils, %	5±2	4±4	5±5	5±3
Eosinophils, %	0.3±0.4	0.6±1	0.7±0.9	0.5±0.7
CD4, %	44±13	72±15	82±13	80±12
CD8, %	32±13	17±8	12±7	13±7
CD4/CD8	1.7±1.0	5.7±4.5	9.3±5.0	8.3±4.8

T lymphocyte subset analysis (CD4/CD8 ratio) of elevated BAL fluid is an important finding in establishing the diagnosis of sarcoidosis. A CD4/CD8 ratio of more than 3.5 shows a high specificity of about 93-96% for sarcoidosis but a low sensitivity of about 53-59%. Therefore, clinical support, typical radiological features of sarcoidosis, and biopsy are required. However, the assessment of CD4/CD8 ratio is still debatable due to the high variability of sarcoidosis.[25,28]

A prospective study determined the cell pattern of BAL fluid in newly diagnosed sarcoidosis patients. This study divided patients into three groups, namely patients who were asymptomatic and did not receive corticosteroid therapy, patients who were symptomatic but not treated, and symptomatic patients who had received corticosteroid therapy. The results showed that patients who did not receive therapy with sarcoidosis symptoms had an increase in lymphocytes and a higher CD4/CD8 ratio than asymptomatic patients. Symptomatic patients who had received corticosteroid therapy had lower lymphocytes and total BAL fluid cell counts than symptomatic patients who did not receive therapy.[27]

CONCLUSION

Bronchoalveolar lavage is a minimally invasive procedure that is safe, easy to operate by operators, and well tolerated by patients. Bronchoalveolar lavage is useful for the diagnosis and treatment of non-infectious lung diseases, such as pulmonary alveolar proteinosis and sarcoidosis.

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CONFLICT OF INTEREST

None.

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