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Eosinophil values in exacerbation and stable chronic obstructive pulmonary disease and its relationship to maintenance therapy in stable chronic obstructive pulmonary disease patients

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Background: Chronic obstructive pulmonary disease (COPD) is characterised by persistent and progressive airflow limitations. The study aimed to determine the relationship between eosinophil values in patients with stable and exacerbated COPD, and the relationship of eosinophil values with two drug regimens used as maintenance therapy in stable COPD.

Materials and methods: This cross-sectional study and the variables used in this study were eosinophil counts in stable and exacerbated COPD patients.

Results: Eighty-three patients with stable and exacerbated COPD were included. Stable COPD (63.9%) was predominant, with the highest degree of symptoms in group A 18 patients (34%) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2; 35 patients (66%). The degree of COPD exacerbation was dominated by Type II COPD 15 patients (50%). Eosinophil counts in patients with stable COPD were less than 100 cells/mm^3 37 patients (44.6%), while in patients with COPD exacerbation, it was greater than 100 cells/mm^3 with a total of 30 patients (36.1%). Long acting muscarinic antagonist class of drugs was the most used treatment as maintenance therapy in stable COPD 34 patients (64.2%).

Conclusion: The eosinophil counts in patients with COPD exacerbation were significantly higher than those in patients with stable COPD. The provision of maintenance therapy in the long acting β-2 agonist + inhaled glucocorticosteroid group of stable COPD patients was generally provided to COPD patients with eosinophil values greater than 100 cells/mm^3, and the provision of long-term maintenance therapy in stable COPD patients was generally given to COPD patients with eosinophil values less than 100 cells/mm^3.

Keywords: COPD exacerbation, COPD stable, eosinophil values, LABA and ICS, LAMA

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable lung disease characterised by a persistent and generally progressive airflow limitation associated with an excessive chronic inflammatory response in the airways and lung parenchyma due to harmful gases or particles[1]. COPD is a lung disease with heterogeneous lung conditions characterised by chronic respiratory symptoms (dyspnoea, cough, sputum production, and/or exacerbations) due to abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, obstruction of airflow[2]. COPD is a major global health problem due to its high prevalence (~10% of the adult population), increased incidence (partly related to population aging), and associated significant personal, social, and economic costs. According to the WHO, COPD is the third highest cause of death globally[3,4].

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According to the Global Initiative for Chronic Pulmonary Disease (GOLD) 2023, patients can be evaluated using the modified British Medical Research Council (mMRC) questionnaire and for more comprehensive questions using the COPD Assessment Test (CAT), which includes eight questions with a score of 0–40. Values 0–10 can be obtained from patients with COPD in a stable state and values greater than 10 from those in an exacerbated state[2]. COPD during acute expansion shows the degree of separation, according to Anthonisen, in the presence of reduced dyspnoea, sputum, and purulent volume.[5]

Eosinophils are commonly found in peripheral blood, and tissues. In some lung diseases, they can be found both in the lung tissue and airway wall or alveolar lumen[1]. Airway inflammation in patients with COPD is an inflammatory response to chronic irritation caused by smoking. International guidelines suggest that the number of blood eosinophils serves as a biomarker to help determine appropriate and effective treatment. Intervention studies have shown that patients with high levels of eosinophilia may respond better to inhaled corticosteroids[6,7]. Additionally, abnormal eosinophils could be caused by several respiratory diseases, including Covid-19 with COPD as comorbidities, especially during a pandemic. On routine laboratory examination for Covid-19 patients, we found lymphocytopenia and increased C-reactive protein levels, while abnormalities from other laboratory tests in cases complicated by coagulopathy included increased D-dimer, thrombocytopenia, a prolonged prothrombin time, increased fibrinogen, increased lactate dehydrogenase, increased ferritin and we use the eosinophil value in this study. The patient has a fever and shows shortness of breath, lesions in the lungs worsen, and lymphocyte count decreases. Increased levels of inflammatory biomarkers and hypercoagulation are noted in this stage as well. The hallmark of severe Covid-19 is the presence of a systemic inflammatory response, and most hospitalised patients with Covid-19 show abnormal inflammation. Evaluation of the levels of inflammation markers, such as C-reactive protein and interleukin-6, aids the management of patients with Covid-19. Several studies have shown that regarding confirmed Covid-19, people with comorbidities, such as the elderly, have a higher risk of experiencing severe and fatal symptoms than those without comorbidities. Furthermore, COPD, hypertension, diabetes mellitus, and heart disease are the most common comorbidities among patients with Covid-19 that have been identified. Therefore, additional examinations and markers of inflammation are required, especially during a pandemic, to make sure that eosinophil abnormalities in stable COPD and exacerbations are not caused by Covid-19[8,9].

The provision of initial treatment in patients with stable COPD and optimal management of exacerbations will have an effect on the success of COPD treatment, which aims to improve health, reduce symptoms, maintain lung function, prevent exacerbations, and reducing mortality[2]. In the eosinophilia group, both the increase in eosinophils in the tissue and in the blood showed a very good response when administered in combination with corticosteroids compared with the administration of long acting β2 agonists (LAMAs)[10]. Therefore, this study aimed to determine the relationship between eosinophil values in patients with stable and exacerbated COPD, and the relationship of eosinophil values with LABA + inhaled corticosteroids (ICS) or LA muscarinic antagonist (LAMA) drugs used as maintenance therapy in stable COPD.

HIGHLIGHTS

- The eosinophil count in patients with chronic obstructive pulmonary disease exacerbation was significantly higher than that in patients with stable Chronic obstructive pulmonary disease.
- The provision of maintenance therapy in the long acting β-2 agonist + inhaled glucocorticosteroid group has eosinophil values less than 100 cells/mm^3.
- The provision of Long acting muscarinic antagonist maintenance therapy has eosinophil values less than 100 cells/mm^3.
- The percentage of eosinophils multiplied by blood leucocyte number was lower than the direct calculation of eosinophil values.

Methods

This study used descriptive analytics, and the research design was cross-sectional, taking secondary data from medical records and eosinophil values in patients with stable and exacerbated COPD. The study included 83 patients as research subjects. The technique for taking research subjects used a total sampling technique because the number of research subjects was not sufficient to carry out research subject calculations using a single population proportion method. Research subjects were collected using the convenience or consecutive sampling method. The research subjects in this study were taken from the entire population that met the inclusion and exclusion criteria. The inclusion criteria in were patients with stable and exacerbated COPD who had complete medical records. Exclusion criteria in this study were patients with incomplete medical record data and medical record numbers, patients with a history of allergies, patients with LABA + ICS + LAMA treatment, LABA treatment patients, patients with a history of Asthma and COPD and patients with age less than and equal to 40 years, because exposure to cigarette smoke for more than 20 years can be found in patients over the age of 40 years old.This study used the χ^2 test to determine the relationship of eosinophil values with patients with stable and exacerbated COPD, and the relationship of eosinophil values with LABA + ICS or LAMA class drug treatment, analysed using computer software through SPSS version 29.0 (Statistical Product and Service Solutions). Written informed consent was obtained from all the participants. This study has been reported online following the STROCSS 2021 criteria[11].

Results

The basic characteristics of patients with exacerbated and stable COPD are listed in Table 1. There were four age groups; the dominant age was 50–59 years, with 38 patients (45.8%). The data also showed that male patients had a higher number of patients (71 patients, 85.5%). The dominant level of education among patients with COPD was the high school group, with 38 patients (45.8%). The dominant type of work was private employee, with 22 patients (26.5%) and the lowest was driver, with three patients (3.6%). Most patients with COPD had a normal BMI, with 54 patients (65%).

Table 1 also shows the risk factors obtained from patients with COPD patients were smoking, totalling 55 patients (66.3%),

Table 1

Characteristics and risk factors of patients with stable and exacerbated COPD.

Patients	Amount (*N*)	(%)
Patients characteristics		
Age (years)		
40–49	12	14.5
50–59	38	45.8
60–69	25	30.1
70–79	8	9.6
Sex		
Male	71	85.5
Female	12	14.5
Education		
No school	1	1.2
Elementary school	20	24.1
Junior high school	18	21.7
High school	38	45.8
Associate's degree	3	3.6
Bachelor's degree	2	2.4
Master's degree	1	1.2
Jobs		
Unemployed	11	13.3
Housewife	10	12.0
Driver	3	3.6
Labour	19	22.9
Private officer	22	26.5
Self-employed	13	15.7
Civil servant	5	6.0
BMI		
Under weight	17	20.5
Normal weight	54	65.0
Over weight	12	14.5
Risk factor		
Smoking		
Smoker	55	66.3
Non-smoker	28	33.7
Smoking habits		
Mild smoker	15	18.1
Moderate smoker	22	26.5
Severe smoker	18	21.7
Respiratory infection		
History respiratory infection	40	48.2
No respiratory infection	43	51.8
Air pollution		
Indoor environment	21	25.3
Outdoor environment	62	74.7
Socio economy		
Good home environment	33	39.8
Solid home environment	50	60.2

COPD, chronic obstructive pulmonary disease.

with the Brinkman index of moderate smokers as the highest degree of smoking, totalling 22 patients (26.5%). Other risk factors included absence of infection in the lower respiratory tract with 43 patients (51.8%) and outdoor air pollution with 62 patients (74.7%). COPD can also occur due to socioeconomic factors in a dense environment, totalling 50 patients (60.2%).

Figure 1 shows that the most common type of COPD occurring was the stable type (53 patients,63.9%). The characteristics of patients with stable COPD are dominated by the highest degree of COPD symptoms in Group A, totalling 18 patients (34%), and

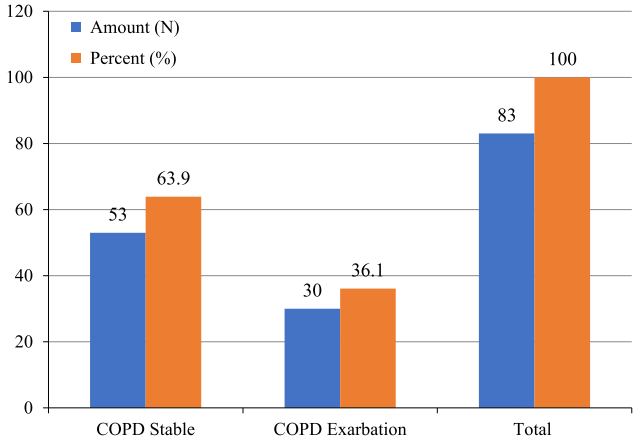

Figure 1. Type of chronic obstructive pulmonary disease (COPD).

the highest classification in COPD was GOLD 2, with 35 patients (66%) (Table 2).

Figure 2 shows that COPD exacerbations are dominated by the moderate degree type with a total of 15 patients (18.1%). Table 3 shows the value of eosinophils in stable COPD is dominated by less than 100 cells/mm^3 with 37 patients (44.6%), while in patients with exacerbated COPD, it is dominated by greater than 100 cells/mm^3 with 30 patients (100%). The most common treatment history in stable COPD patients is the treatment with LAMA class drugs as maintenance therapy (34 patients, 64.2%) (Fig. 3).

The results of the bivariate analysis using χ^2 in this study type of COPD on eosinophil values (Table 4). There was a significant correlation between both patients with stable and exacerbated COPD with eosinophil values greater than 100 cells/mm^3 and less than 100 cells/mm^3 ($P = 0.000$), respectively. χ^2 bivariate analysis of the type of treatment for stable COPD as maintenance therapy with eosinophil values (Table 5) showed statistically significant results, where 16 patients with stable COPD used LABA + ICS drugs as maintenance therapy among patients with eosinophil values less than 100 cells/mm^3. Stable COPD using LAMA class drugs as maintenance therapy was observed in 21 patients (40.5%) with less than 100 cells/mm^3 ($P = 0.040$).

Table 2

Characteristics of stable COPD.

Patients	Amount (*N*)	(%)
Degrees of COPD symptoms		
Group A	18	34
Group B	8	15.1
Group C	11	20.7
Group D	16	30.2
Classification of COPD		
GOLD 1	4	7.5
GOLD 2	35	66
GOLD 3	13	24.6
GOLD 4	1	1.9

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Pulmonary Disease.

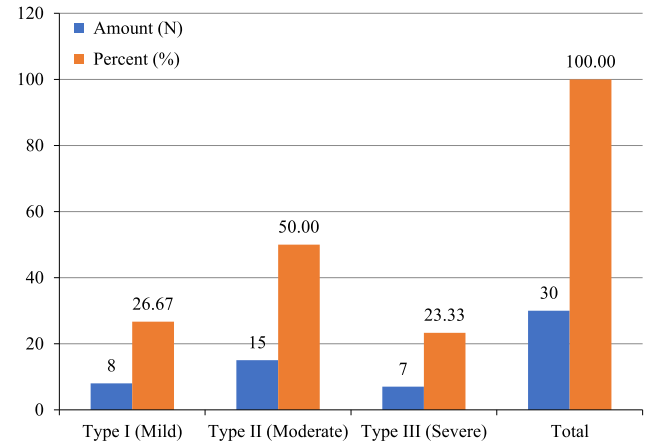

Figure 2. COPD exacerbation. COPD, chronic obstructive pulmonary disease.

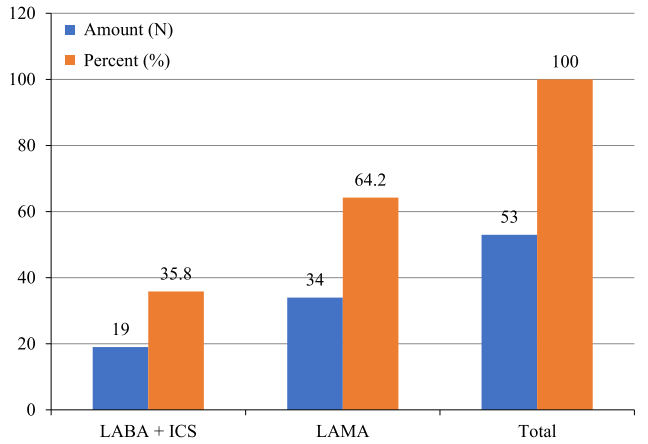

Figure 3. Stable COPD treatment history with LABA + ICS and LAMA as maintenance therapy. COPD, chronic obstructive pulmonary disease; ICS, inhaled glucocorticosteroid; LABA, long acting β-2 agonist; LAMA, long acting muscarinic antagonist.

Discussion

This study found that age group of 50–59 years (45.8%) was more prevalent in patients with COPD. This is in line with Marc Miravitlles and colleagues, who found that patients with COPD taking LAMA/LABA/ICS drugs were more common at the age of less than 65 years, at 45.3%[11]. COPD often occurs in the 50-year-old age group because of a decrease in lung function or changes in internal organs[12]. In this study, 85.5% of the patients with COPD were males. This is in line with Hurst and colleagues, who found that the male sex has a greater prevalence of COPD (85.3%). Men are more likely to develop COPD than women because men have a much higher prevalence of smoking than women, given that smoking is a major factor in COPD[13,14]. In this study, the highest education level among patients with COPD was high school (45.8%). This is in line with Alawiyah *et al.*[15] that the highest level of education in patients with COPD was high school, at as much as 40%. In addition, the dominant work among patients with COPD was the type of work as a private employee, which is as much as 26.5%. This is in line with Asyrofy *et al.*[16] which reported the highest employment rate in patients with COPD as private employees (42.9%). Normal BMI (65%) dominated in this study among patients with COPD. This is also in line with research conducted by Wu *et al.*[17], who obtained the highest BMI in the normal-weight group (49%).

In the present study, various risk factors were found to cause COPD. First, the occurrence of COPD was a risk factor for smoking with a prevalence of 66.3%. This is in line with Zhu and colleagues, which found that smoking was the greatest risk factor (64.5%). Repeated oxidative stress and continuous inflammation can cause extensive tissue damage, resulting in disease susceptibility[18,19]. The smoking groups derived from the Brinkman Index were predominantly moderate smokers (16.5%). This is in line with Alawiyah *et al.*[15], which found the highest proportion of moderate smokers among patients with COPD compared with other groups of smokers (37.1%). Lower airway infection is a risk factor for COPD; however, in this study, it was dominated by the group that did not have a history of lower airway infection (51.8%). This is in line with the research conducted by Rasyid and colleagues, in which the group that did not have a history of lower respiratory tract infections was the highest (55.8%). Air pollution is also a risk factor for COPD, and the group with the highest risk of air pollution was the group with a history of outdoor air pollution of as much as 74.7%. This is in line with the research conducted by Rasyid *et al.*[13], who proved that outdoor air pollution is the highest group compared to indoor air pollution, which is as much as 60.5%. The socio-economically dense environment was the most common group in this study, with a total of 60.2%. This is in line with the research conducted by Samosir and colleagues, who conducted his research on a patient, who suffers from COPD and has a solid socioeconomic environment. Such dense environments generally have a high risk of dirty air pollution; therefore, the air is inhaled continuously which can cause obstructive breathing disorders[20].

Table 3

Eosinophils values of COPD stable and exacerbations groups.

Patients	Amount (*N*)	(%)
COPD stable		
> 100 cell/mm^3	16	19.3
< 100 cell/mm^3	37	44.6
COPD exacerbations		
> 100 cell/mm^3	30	36.1
< 100 cell/mm^3	0	0.0
Total	83	100

COPD, chronic obstructive pulmonary disease.

Table 4

Comparison of eosinophil values with stable and exacerbation type COPD.

	Values eosinophils				
	< 100 cell/mm^3		> 100 cell/mm^3		
Type COPD	*N*	%	*N*	%	*P*
COPD stable	37	44.6	16	19.3	0.000
COPD exacerbation	0	0.0	30	36.1	

COPD, chronic obstructive pulmonary disease.

Table 5

Comparison of eosinophil values in patients with stable COPD treated with LABA + ICS or LAMA as maintenance therapy.

	Values eosinophils				
	< 100 cell/mm^3		> 100 cell/mm^3		
Treatment COPD	N	%	N	%	P
LABA + ICS	3	3.8	16	30.7	0.040
LAMA	13	25	21	40.5	

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long acting β2 agonist; LAMA, long acting muscarinic antagonist.

The type of COPD in this study was dominated by stable COPD compared to COPD exacerbation (63.9%). This is in line with a study conducted by Schufmann *et al.*[21], who found that the value of stable COPD was higher than that of exacerbated COPD (74.9%). In this study, mMRC or CAT helped determine the degree of symptoms in stable COPD patients; the highest degree or Group A Group A compared to the other groups (34%). This is in line with the research conducted by Huib and colleagues, where Group A occupied the highest group (29.6%)[22]. In addition, the degree of COPD in this study was highest in the COPD GOLD 2 group (66%). This is in line with the research conducted by Fachri *et al.*[23], who obtained the highest group of degree 2 COPD which was 32.43%.

Based on previous studies, respiratory diseases might alter the haematological profiles, including erythrocytes, leucocytes, eosinophils, thrombocytes, and erythrocyte sedimentation rate. These haematological abnormalities could impact the diagnosis, prognosis, and therapeutic response[24]. Since eosinophilia is generally a hallmark of asthma, recent studies have found that eosinophilia can occur in patients with COPD during exacerbations and in the presence of airway infections[25].

The eosinophil count in patients with COPD exacerbation was higher in the greater than 100 cells/mm^3 group than in the less than 100 cells/mm^3 group (36.1%). This is in line with Bruselle *et al.*[26], which had the highest group count and high eosinophil values in patients with COPD exacerbation, about 70% of adult patients with eosinophil values greater than 2%.

The history of treatment administered to COPD patients in this study included two groups: the LABA + ICS treatment group and the LAMA treatment group. The highest treatment rate was observed in the LAMA group (64.2%). However, this is not in line with So Young Park's research, which obtained the highest treatment group for the LABA + ICS type (50.8%). LABA + ICS is used more often because this type of treatment can inhibit the development of inflammation compared with other types of treatment[27].

In this study, we investigated the types of COPD and COPD exacerbations with eosinophil values greater than 100 cells/mm^3 and less than 100 cells/mm^3. When researching these two variables, a bivariate study was conducted using the χ^2 test, where the *P* value was 0.000, which means that the value of eosinophils in patients with COPD exacerbation was much higher than the value of eosinophils in stable COPD patients. This is in line with a study conducted in the USA, which showed that eosinophil values increase in patients with COPD exacerbations. Increased eosinophil values in COPD patients can be exacerbated because eosinophils are inflammatory mediators that move on the airway wall affected by cytokines together with prostaglandins[28].

In this study also conducted a study that aims to find the relationship between the type of treatment LABA + ICS or LAMA with the number of eosinophils greater than 100 cells/mm^3 and less than 100 cells/mm^3. When researching these two variables, a bivariate study was conducted using the χ^2 test, where the *P* value was 0.04, which means that treatment with LABA + ICS drugs is generally given to stable COPD patients who have increased eosinophil values or greater than 100 cells/mm^3, and treatment using LAMA group drugs is generally given to stable COPD patients with eosinophil values of less than 100 cells/mm^3. This is in line with research conducted in Korea, which explained that stable COPD patients with eosinophil values greater than 100 cells/mm^3 are generally administered LABA + ICS Group drugs as maintenance therapy. Because in stable COPD patients who have eosinophil values greater than 100 cells/mm^3 who generally use LABA + ICS drugs will provide more optimal benefits compared to the provision of LAMA drugs[29,30]. Singh *et al.*[29] found that stable COPD patients with eosinophil values greater than 100 cells/mm^3 were generally administered LABA + ICS drugs; in this study, stable COPD patients with eosinophil values of less than 100 cells/mm^3 were generally administered LABA + ICS drugs. In stable COPD patients described in the study by Bartziokas *et al.*[30], LAMA drugs can be administered to patients who have eosinophil values of more than 100 cells/mm^3; however, in this study, stable COPD patients with eosinophil values of less than 100 cells/mm^3 were generally administered LAMA drugs. In this study has a limited number of subjects who are still relatively few despite meeting the required number of subjects. As another limitation of this study, it is acknowledged that the small sample size negates the generalisation of this study. In this study, we also used the eosinophil count value based on the percentage of eosinophils multiplied by the number of blood leucocytes, where the value had a lower significance than the direct calculation of eosinophil values. In addition, the data obtained from medical records still lack a good technique for diagnosing diseases with different aetiologies, incomplete medical record data such as patient identity, risk factors contained in the medical records, or laboratory results. Therefore, there is still much data that can be used as a subject of research because the data are incomplete, and not all risk factors that are in the medical records entered by the researcher in this study.

Conclusion

The eosinophil count in patients with COPD exacerbation was significantly higher than that in patients with stable COPD ($P = 0.00$). The provision of maintenance therapy in the LABA + ICS Group in stable COPD patients was generally given to COPD patients with eosinophil values less than 100 cells/mm^3, and the provision of LAMA maintenance therapy in stable COPD patients was generally given to COPD patients with eosinophil values less than 100 cells/mm^3, which was statistically significant ($P = 0.04$).

Ethical approval

This study was approved by the Ethics Committee of the Faculty of Medicine and Health, Universitas of Muhammadiyah Jakarta, at the Faculty of Medicine and Health, Universitas of Muhammadiyah Jakarta, Jakarta Indonesia (No.406/PE/KE/FKK-UMJ/XII/2022). Written informed consent was obtained from all the participants.

Consent

NA.

Sources of funding

NA.

Author contribution

M.F., M.H., M.A., F.F., R.A., and A.W. conceived and designed the study, conducted research, provided materials, and collected and organised data. M.F., F.I.L., F.F., M.H., Y.A., R.S., and A.S. drafted the manuscript. M.F., F.F., A.S., M.R.P., R.D., A.A., A.F., A.A., and M.H. Analysed the data and interpreted data. M.F., M.H., M.R.P., R.A., F.I.L., A.R.J., A.F., A.W., A.A., and M.H. wrote initial and final draft article, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique Identifying number (UIN) or registration ID: researchregistry8896 at April 25, 2023.
3. Hyperlink to specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/64470cf1e4ddb40027efecb3/.

Guarantor

Prof. Mochammad Hatta.

Data availability statement

Datasets generated during and/or analysed during the current study are publicly available.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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