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Decreased Levels of Serum IgE and Periostin, Length of Stay (LOS) in COPD Exacerbation Inpatients Following Pulmonary Rehabilitation and Early Short Wave Diathermy (SWD) Modality Therapy - A Quasi Experimental Trial

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Abstract:- Early pulmonary rehabilitation is beneficial for patients hospitalized with COPD Exacerbation. It reduces the risk of re-hospitalizations and improves quality of life. This study aims to analyze the effectivity of pulmonary rehabilitation and modality therapy on reducing serum IgE, Periostin, and Length of Stay (LOS) of hospitalized COPD exacerbated patients, which has never been studied in Indonesia. Quasi-experimental design of COPD exacerbated patients was differentiated based on ROME Proposal. Hospitalized in Saiful Anwar and Lawang Hospital in 2023 with pre and post-test were done in each group with total 24 sample. Subjects were divided into three groups; first group was given standard therapy of COPD exacerbation, pulmonary rehabilitation therapy for the second and SWD for the third. There was a significant difference between the three groups (p=0.000), all variables having significant decrease level of level in the combined pulmonary rehabilitation and SWD modality therapy group. There was a strong positive correlation of Serum IgE and Periostin (r=0.856, p=0.000), moderate negative correlation of Serum IgE and LOS (r=-0.591, p=0.002), and moderate negative correlation of Periostin and LOS (r=-0.592, p=0.002). In conclusion, there was significant decrease of Serum IgE and Periostin in early combined pulmonary rehabilitation and SWD group, making it a non-pharmacological therapy option and recommended to reduce LOS in patients with COPD exacerbations.

Keywords*: Serum IgE, Periostin, LOS, COPD Exacerbation, SWD Therapy.*

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) exacerbations are one of the causes of patients to be hospitalized with a progressive decrease in lung function and repeated exacerbations which then increases the morbidity and mortality rates of patients[1]. These exacerbations are associated with progressive lung function decline, increased morbidity, and higher mortality rates. Therefore, a combination of appropriate pharmacological and non-pharmacological management is needed to reduce COPD symptoms and enhance the quality of life of the patients[2]. Non-pharmacological interventions such as pulmonary rehabilitation and modality therapies have been explored for their potential to reduce hospital stays and complementary to pharmacological therapy and remain

part of the comprehensive management of COPD[3]. COPD is a major challenge in public health today[12]. According to Indonesian Ministry of Health in 2019, COPD is one of the four major non-communicable diseases that cause death in Indonesia. According to Riskesdas data in 2018, the prevalence of COPD in Indonesia was 3.7% and was more common in men. Meanwhile, in East Java, the prevalence of COPD is 3.6%. Based on World Health Organization (WHO) data, 2.9 million people died from COPD and it is estimated that by 2030, COPD will become the third cause of death in the world.

Pulmonary rehabilitation is a comprehensive intervention involving various aspects, including education, exercise training, and behavior change, which has been shown to provide consistent benefits and is the main non-pharmacological management in patients with stable COPD according to the GOLD 2023 guideline[1]. In addition, many previous studies on pulmonary rehabilitation in COPD exacerbations that have been updated with the addition of 11 new studies in the systematic review database by Cochrane and Puhan in 2016. Pulmonary rehabilitation can be performed during hospitalization and/or outpatient care, but should be started immediately or within 3 weeks after starting treatment for COPD exacerbations. The results of these studies overall suggest that pulmonary rehabilitation is safe, and there is no evidence of increased mortality. Currently, there is no treatment that can cure COPD, therefore, management of the disease should include the use of pharmacological and non-pharmacological medications that can prevent physical function decline and improve the Health Related Quality of Life (HRQoL) of patients with COPD[8][12].

Although there are not enough studies explaining the benefits of pulmonary rehabilitation in patients with COPD exacerbations, some previous studies have explained that pulmonary rehabilitation in patients with acute COPD exacerbations is safe, effective, and can improve exercise endurance and Quality of Life (QoL). Therefore, it is proposed that comprehensive pulmonary rehabilitation measures should be implemented immediately after the onset of an acute exacerbation, in the hope of improving exercise ability, activity and QoL of patients[12].

COPD exacerbations make an inflammation process and increase of some inflammation marker such as IgE and Periostin. Periostin is an extracellular matrix protein that is produced and plays an important role in tissue remodeling. Periostin may be a biomarker of type 2 inflammation in COPD exacerbations. In airway diseases, the role of periostin has been extensively investigated in patients with bronchial asthma. It has been demonstrated that this mesenchymal protein is secreted by bronchial epithelial cells and pulmonary fibroblasts serving as a basic component of subepithelial fibrosis in asthmatic patients. Its expression is upregulated by type 2 cytokines Interleukin-14 (IL-4) and Interleukin-13 (IL-13). In addition, serum periostin has been recognized as a marker of Th2 inflammatory response in the airways of asthmatic patients and has been associated with eosinophilic inflammation. Previous studies have shown that serum periostin concentration can be used as a marker of airway remodeling in adult severe asthma and COPD patients[9].

Allergic reactions have been proposed as a common factor in patients with asthma and COPD. At present, the role of allergy in the pathogenesis of asthma has been commonly recognized, but its role in COPD has not been widely studied. Immunoglobulin E (IgE) in the blood has been the focus of research due to its role in asthma. The results showed that blood IgE could be a potential biomarker to predict the risk of exacerbations in a subset of patients with COPD. These findings may help in the development of more effective exacerbation prevention strategies and improve the management of COPD patients, thus predicting the length of hospital stay[13]. Based on that, researchers are interested in knowing the effectiveness of pulmonary rehabilitation and modality therapy on reducing serum periostin, serum Ig-E, and LOS (Length of Stay) of hospitalized COPD exacerbation patients. This study has never been done in Indonesia before and researchers hope that it can be a reference for additional management in order to reduce the mortality rate of COPD exacerbation patients.

2. Method

This study was conducted from December, 2022 to May, 2023. This research design is a quasi-experimental study with pre-post test group and single-blind randomization. The subjects in this study were patients with COPD who had been previously established through a comprehensive examination, who experienced an exacerbation and came to the Emergency Room and were hospitalized at Dr. Saiful Anwar Hospital and Lawang Hospital, East Java, Indonesia.

The selection of research subjects used consecutive sampling method and was selected based on the inclusion criteria:

- Patients aged 18-65 years
- Diagnosed with COPD exacerbation defined as an event characterized by dyspnea and/or cough with sputum that worsen over <14 days based on ROME Proposal
- Undergoing non-intensive hospitalization.
- Willingness to participate and sign informed consent on this study.

Meanwhile, the exclusion criteria:

- Presence of acute or chronic cerebrovascular disease.
- History of active hemoptysis within the last three months.
- Malignancies in the thoracic cavity.
- Lung tuberculosis.
- Exacerbation of asthma.
- Asthma-COPD overlap.

There were 24 research subjects who met the inclusion and exclusion criteria. The study subjects were then divided into three groups by single-blind randomization, namely the control group, the intervention group with pulmonary rehabilitation only, and the intervention group that underwent pulmonary rehabilitation combined with SWD therapy. Baseline data collection was carried out on the first day of admission including basic complete blood laboratory examination and chest x-ray. After that, venous blood samples were taken for examination of serum IgE and Periostin levels using the IgE ELISA Kit 96T and Human POSTN/OSF-2 ELISA Kit 96T. On the fifth day of treatment, evaluation and venous blood collection for IgE and Periostin inflammatory markers were carried out to be recorded and analyzed in relation to the patient's Length of Stay (LOS) until hospital discharge.

Pulmonary rehabilitation includes Breathing Exercise for 10 minutes - 1 hour per session 2-3x/day, Clapping and Vibration 5 min per lung lobe repeated until all lobes, Effective Coughing Technique 2x/day, Postural Drainage 2 hours before meals, and modality therapy with Short Wave Diathermy (SWD) at 27,12 MHz, 2x a day until patient discharged. The pulmonary rehabilitation therapy procedures continue to be carried out by Physiatrists and Physiotherapists who have been trained in the treatment group starting from the first day and during the patient's hospitalization.

The data obtained were then analyzed into characteristic data of the research results presented in the form of mean + SD and continued with several statistical tests, namely Normality Test with Saphiro Wilk, Differential Test between groups with One Way ANOVA, Paired T-Test Test, Pearson Correlation Test followed by Post Hoc Tuckey and Dunn Test. Data processing and analysis were done using IBM SPSS software version 24.0 that yield confidence level 95%, significance α 0.05 and research power 80%.

3. Result

During the research period, there were 24 subjects who participated in the study until the end. Of the 24 subjects, 8 subjects received standard COPD Exacerbation therapy in the form of medication as a control group, 8 subjects received medication therapy and additional pulmonary rehabilitation, and 8 other subjects received medication therapy, pulmonary rehabilitation and additional therapeutic modalities using Short Wave Diathermy (SWD).

Table I. Characteristics of Subject

Characteristics	Frequency (n)	Percentage (%)	Mean±SD
Gender			
Male	15	62.5%	
Female	9	37.5%	
Age			
<50 years	3	12.5%	57.83 ± 5.75
>50 years	21	87.5%	Min- Max 45-65
Smoking status			
Active smoker	13	54.2%	
Passive smoker	8	33.3%	
Not smoking	3	12.5%	
Brinkman Index			
<200 (Mild smoker)	0	0%	
200-599 (Moderate smoker)	11	84.6%	
>600 (Severe smoker)	2	15.4%	
Pollution Exposure History			
Outdoor	13	54.2%	
Indoor	7	29.1%	
Not at all	4	16.5%	
Exacerbation Degree			
Mild	2	8.3%	
Moderate	18	75.0%	
Severe	4	16.7%	
Comorbid			
HF (*Heart Failure*)	3	12.5%	
DM (*Diabetes Mellitus*)	1	4.1%	
Pneumonia	5	20.8%	
HF and Pneumonia	2	8.3%	
DM and Pneumonia	3	12.5%	
Others	10	41.7%	
mMRC Pre Treatment			
Grade 1	0	0%	
Grade 2	4	16.5%	
Grade 3	19	79.1%	
Grade 4	1	0.04%	
mMRC Post Treatment			
Grade 1			
Grade 2	14	58.4%	
Grade 3	8	33.3%	
Grade 4	2	8.3%	
	0	0%	
CAT score Pre Treatment			
<10	0	0%	
>10	24	100%	
CAT score Post Treatment			
<10	17	70.8%	
>10	7	29.2%	

Based on Table I. above, it shows the demographic characteristics of 24 research subjects consisted of 62.5% (15 people) men and 37.5% (9 people) women. This is in accordance with Riskesdas data in 2018 that the prevalence of COPD in Indonesia is 3.7% and is more common in men. The prevalence of COPD in East Java is 3.6%, slightly below the national average. The age distribution in this study showed that the majority of 87.5% (21 people) of the research subjects were aged> 50 years and the remaining 12.5% (3 people) were <50 years old. Smoking status is then associated with the incidence of COPD exacerbations according to the results in this study as many as 13 people (54.2%) of the study subjects were active smokers. From active smokers we have, the most subjects with Index Brinkman 200-599 as 11 subjects (84.6%). The most history of pollution exposure in this study is outdoor pollution exposure was 54.2% (13 people) and indoor pollution was 29.1% (7 people). Based on exacerbation degree, the most subjects in moderate degree (75%), severe degree as 4 subjects (16.7%), and mild degree as 2 subjects (8.3%). In this study, it was found that the comorbidities suffered by the most subjects were pneumonia as many as 5 subjects (20.8%), HF as many as 3 subjects (12.5%), DM and Pneumonia as many as 3 people (12.5%), and other comorbidities as many as 10 subjects (41.7%).

Table II: Mean of Serum Periostin and IgE Levels and LOS in Pre and Post Treatment Variables

IgE Serum		
Group (n=24)	**Pre treatment mean (pg/ml)**	**Post treatment mean (pg/ml)**
Control (CO)	1.39	1.52
Pulmonary Rehabilitation only (PR)	1.51	0.80
Pulmonary Rehabilitation & SWD (SWD)	1.29	0.36
P Value	**p =0.827**	**p=0.000**

Periostin Serum		
Group (n=24)	**Pre treatment mean (pg/ml)**	**Post treatment mean (pg/ml)**
Control (CO)	11.49	11.41
Pulmonary Rehabilitation only (PR)	11.97	7.51
Pulmonary Rehabilitation & SWD (SWD)	11.24	3.90
P Value	**p = 0.770**	**p=0.000**

Length of Stay (LOS)	
Group (n=24)	**LOS Mean (days)**
Control (CO)	6.93
Pulmonary Rehabilitation only (PR)	4.75
Pulmonary Rehabilitation & SWD (SWD)	2.88
P Value	**p=0.007**

Table II shows the average of each research variable before and after standard therapy or treatment consisting of 3 variables studied in each group. In the first variable, mean level of Serum IgE, increased in the control group with a pre-therapy level of 1.39 and a post-therapy level of 1.52. In the treatment group with pulmonary rehabilitation, there was a decrease in serum IgE levels after treatment with pre-therapy levels of 1.51 and post-therapy levels of 0.80. This level decreased significantly in the group with pulmonary rehabilitation treatment alone. In contrast to the pulmonary rehabilitation treatment group plus SWD modality therapy, there was a decrease in serum IgE levels which turned out to be more significant with pre-therapy levels of 1.29 and post-therapy levels of 0.36. This means that the most significant value in serum IgE levels in this group compared to the other two groups that were only given standard therapy or treatment with pulmonary rehabilitation alone.

The second variable, Serum Periostin, can be observed based on the table above, has almost the same average level in the control group with pre-therapy levels of 11.49 and post-therapy levels of 11.41. In the treatment group with pulmonary rehabilitation, there was a decrease in serum Periostin levels after treatment with pre-therapy levels of 11.97 post-therapy levels of 7.51. In contrast to the pulmonary rehabilitation treatment group plus SWD modality therapy, there was a twice significant decrease in serum Periostin levels with pre-therapy levels of 11.24 and post-therapy levels of 3.90. This means that the most significant value decrease in serum Periostin levels in this group compared to the other two groups that were only given standard therapy or treatment with pulmonary rehabilitation alone.

The third variable observed was Length of Stay (LOS) in the subject, it can be observed based on the table above, having a mean LOS of 6.93 days in the control group. In the treatment group with pulmonary rehabilitation, there was a decrease in the average LOS to 4.75 days. In contrast to the pulmonary rehabilitation treatment group plus SWD modality therapy, there was a more significant decrease in LOS, which was only an average of 2.88 days compared to the other two groups.

Table III: Pairwise Comparisons Test between each groups

Comparison of IgE Post Each Group	p value
IgE CO vs IgE PR	**0.000**
IgE CO vs IgE SWD	**0.034**
IgE EX vs IgE SWD	**0.034**

Table III shows, the comparison results for IgE Post in the CO group, it shows that it is significantly different from IgE Post in the PR group (p=0.000), and IgE Post in the SWD group (p=0.034). Comparison of IgE Post in the PR group is significantly different from IgE Post in the SWD group (p=0.034).

Table IV: Pairwise Comparisons Test between each groups

Comparison of Periostin Post Each Group	p value
Periostin CO vs Periostin PR	**0.000**
Periostin CO vs Periostin SWD	**0.000**
Periostin PR vs Periostin SWD	**0.000**

Notes: Significant if p<0.05

Table IV shows, the comparison results for Periostin Post in the CO group showed a significant difference compared to the PR group (p=0.000), and the SWD group (p=0.000). Comparison of Periostin Post in the PR group is significantly different from the PR group (p=0.000).

Table V: Pairwise Comparisons Test between each groups

Comparison of LOS Each Group	P value
LOS CO vs LOS PR	**0.002**
LOS CO vs LOS SWD	**0.050**
LOS PR vs LOS SWD	**0.040**

Notes: Significant if p<0.05

Table V shows, the comparison test for LOS in the CO group showed a significant difference compared to LOS in the PR and SWD groups (p=0.002 and p=0.050), as well as LOS in the PR group showed a significant difference to LOS in the SWD group (p=0.040).

Table VI: Difference Test between each groups

Variable	CO n = 8 Mean± SD	PR n = 8 Mean± SD	SWD n = 8 Mean± SD	p-value
Decrease of IgE Serum	-0.148 ±0.258	0.492 ±0.141	1.151± 0.485	**0.000**
Decrease of Periostin Serum	0.028 ±0.734	3.726 ±0.928	8.068 ± 1.262	**0.000**
Length of Stay (LOS)	6.93 ±1.309	4.75 ±0.886	2.88 ± 0.834	**0.002**

Notes: Significant if p<0.05

The results of ANOVA analysis in Table VI, showed a significant difference of decreasing IgE serum, Periostin serum and LOS between the control group, the group with pulmonary rehabilitation and the group with pulmonary rehabilitation plus modality therapy. Based on the first variable studied, namely serum IgE, the results show significant p= 0.000, followed by serum Periostin results with p= 0.000, and Length of Stay with p=0.002.

The first variable, serum IgE, can be seen in the control group with an average value of -0.148 ± 0.258, while the pulmonary rehabilitation group has an average value of 0.492 ± 0.141, and the pulmonary rehabilitation group plus modality therapy has an average value of 1.151 ± 0.485. The obtained P-value of p = 0.000 shows a significant difference between the three groups. The second variable is the decrease in serum Periostin, based on Table 6 above, the control group has an average value of 0.028 ± 0.734, the pulmonary rehabilitation group has an average value of 3.726 ± 0.928, and the pulmonary rehabilitation group plus modality therapy has an average value of 8.068 ± 1.262. The very low P-value (p = 0.000) indicates a significant difference between the three groups. The third variable, namely Length of Stay (LOS), obtained results in the control group had an average value of 6.93 ± 1.309, the pulmonary rehabilitation group had an average value of 4.75 ± 0.886, and the pulmonary rehabilitation group plus modality therapy had an average value of 2.88 ± 0.834. The P-value of p = 0.002 showed a significant difference between the three groups based on the length of hospitalization.

Based on these three results, researchers can conclude that the group with pulmonary rehabilitation plus modality therapy and the group with pulmonary rehabilitation therapy alone have a significant effect on the treatment variable compared to the control group which is only given standard COPD exacerbation therapy. This can be seen based on the decrease in Serum IgE, Serum Periostin, and Length of Stay in patients. Analysis of the mean decrease in the Pulmonary Rehabilitation Group plus Modality Therapy showed the highest average decrease in all three variables measured. Specifically, there was a significant decrease in Serum IgE by 1.151, a decrease in serum Periostin by 8.068, and the lowest duration of hospitalization, which was 2.88. Thus, the results showed

that the combined intervention of Pulmonary Rehabilitation and SWD Modality Therapy could potentially have a more positive impact on the three parameters observed compared to the other groups.

Table VII: Correlation Analysis between Serum IgE, Serum Periostin, and LOS Variables

Variables	r value	Correlation strength	p-value	Correlation direction
Decreased of Serum IgE and Serum Periostin	0.856	Strong	**0.000**	Positive
Decreased of Serum IgE and Length of Stay	-0.591	Medium	**0.002**	Negative
Decreased of Serum Periostin and Length of Stay	-0.592	Medium	**0.002**	Negative

Notes: Significant if $p<0.05$

The correlation test was carried out with the aim of knowing the correlation between the variables studied. Pearson correlation is used to evaluate the strength and direction of the linear relationship between two variables. The basis for decision making used in correlation testing is to use the significance value (p-value). The Pearson correlation test results in Table VII show that there is a relationship between the variables measured.

The first result based on Table VII, is that there is a strong positive correlation between Serum IgE Decrease and Serum Periostin ($r = 0.856$, $p = 0.000$). This indicates that the presence of a decrease in Serum IgE is concurrently associated with a significant decrease in Serum Periostin. The strength of this strong relationship indicates that a change in one variable is likely to be followed by a comparable change in the other variable. The second result is a moderate negative correlation between Serum IgE Decrease and Length of Stay ($r = -0.591$, $p = 0.002$). This means that the higher the Serum IgE Decrease, the shorter the duration of hospitalization tends to be. This relationship shows a tendency that an increase in Serum IgE coincides with a decrease in the duration of hospitalization. The third result based on the table is that there is also a moderate negative correlation between Serum Periostin Decrease and Length of Stay ($r = -0.592$, $p = 0.002$). This indicates that the higher the Serum Periostin Decrease, the shorter the duration of hospitalization. The moderate strength of this relationship indicates that changes in Serum Periostin correlate with changes in the duration of hospitalization, although not as strong as the relationship between Serum IgE and Serum Periostin.

4. Discussion

4.1 Analysis of Differences in Serum Periostin Levels between Groups

Based on the comparison data of Periostin Pre levels between the 3 groups studied, the p value was 0.770 ($p>0.05$), so it can be concluded that Periostin Pre between groups has no significant difference, because the difference in mean periostin levels in the three groups does not differ too much. The comparison of Periostin Post between the 3 groups observed by the ANOVA test obtained a p value of 0.000 ($p <0.05$), so it can be concluded that Periostin Post between the three groups there is a significant difference. Based on the comparison results for Periostin Post in the CO group showed a significant difference compared to the PR group ($p=0.000$), and the SWD group ($p=0.000$). Comparison of Periostin Post in the PR group is significantly different from the PR group ($p=0.000$).

This is supported by the research of Sidhu *et al*. in the year showed that Periostin levels were found to increase in Exacerbated COPD patients and correlated with disease severity[10]. In the context of pulmonary rehabilitation, this study showed a significant decrease in Periostin levels, reflecting improvements in the inflammatory process and remodeling of lung tissue. Another study conducted by Shirai *et al*. examined inflammatory biomarkers in COPD patients to understand the role of inflammation in disease pathogenesis and progression. Their study evaluated the levels of serum periostin, peripheral blood eosinophils, and several inflammatory cytokines such as IL-5 and IL-13[9]. This is consistent with a previous study conducted by Konstantelou *et al*. who evaluated serum periostin as a predictor of outcome in COPD patients hospitalized for exacerbations[3]. Serum periostin was measured when patients were hospitalized and at discharge. Patients were monitored for 1 year for future

exacerbations, hospitalization, and death. The results showed that the level of periostin at hospital admission was higher than at discharge. Thus, their results suggest that the role of serum periostin as a predictive biomarker of future risk in hospitalized COPD patients is of limited value[3].

4.2 Analysis of Differences in Serum IgE Levels between Groups

Comparison of IgE Pre results between three groups observed using the Kruskal Wallis Test obtained a p value of 0.827 (p>0.05), so it can be concluded that between groups IgE Pre there is no significant difference, because the difference in mean IgE Pre between groups does not differ too much. While in the comparison of IgE Post in the three groups observed using the Kruskal Wallis Test, the p value was 0.000 (p <0.05), so it can be concluded that IgE Post between groups has a significant difference. Based on the comparison results for IgE Post in the CO group, it shows that it is significantly different from IgE Post in the PR group (p=0.000), and IgE Post in the SWD group (p=0.034). Comparison of IgE Post in the PR group is significantly different from IgE Post in the SWD group (p=0.034).

The findings of this study are in line with those found in a study conducted by Xie *et al*., where they showed that a decrease in serum IgE levels was associated with a shorter duration of hospitalization in COPD patients. They evaluated the association between serum Total IgE (T-IgE) levels and clinical characteristics in patients with Exacerbated COPD (ECOPD). The study included 285 ECOPD patients who were admitted to Liaocheng People's Hospital from July 2018 to July 2019. Their results showed that 49.82% of patients had high T-IgE levels (>60 kU/L). Patients with high T-IgE levels had a shorter hospitalization duration (9.49 ± 3.05 days) compared to patients with low T-IgE levels (10.59 ± 3.42 days). After adjustment for confounding factors, T-IgE was negatively associated with the duration of hospitalization[11].

4.3 Analysis of Differences in Length of Stay (LOS) between Groups

In this study, a comparison of Length of Stay (LOS) among three groups observed (CO, PR, and SWD) with the Kruskal Wallis Test obtained a p value of 0.007 (p <0.05), so it can be concluded that there is a significant difference in LOS between groups, with the longest average LOS in the CO group (mean=6.93 days), the shortest LOS in the SWD group (mean=2.88 days). Because there is a significant difference, it is necessary to continue with the Pairwise Comparisons Test (Dunn Test). Based on the results of the comparison test for LOS in the CO group showed a significant difference compared to LOS in the PR and SWD groups (p=0.002 and p=0.050), as well as LOS in the PR group showed a significant difference to LOS in the SWD group (p=0.040).

Based on these results, it can be concluded that LOS showed a significant decrease in the PR group and more significantly in the SWD group. The average LOS was 6.93 days in the CO group, reduced to 4.75 days in the PR group, and 2.88 days in the SWD group. This suggests that this intervention is not only effective in reducing the levels of inflammatory biomarkers such as serum IgE and Periostin but also in shortening the duration of hospitalization, indicating a faster recovery in patients with exacerbated COPD. This reduction in inflammatory biomarker levels and LOS indicates that this intervention not only helps in clinical management but also has the potential to improve overall healthcare efficiency. A study conducted by Li *et al*. highlighted that the use of pulmonary rehabilitation during hospitalization was associated with longer LOS, possibly due to more severe clinical conditions in patients requiring pulmonary rehabilitation. Other factors such as age, gender, and smoking history were also found to play a role in influencing LOS in their study[4]. This study supports the importance of early intervention and effective comorbidity management in reducing LOS and improving clinical outcomes in COPD patients. Further studies are needed to explore optimal strategies in COPD management for various patient subgroups.

4.4 Analysis of correlation between each variables

In this study, there was a strong positive correlation between decreased serum IgE levels and serum Periostin with a correlation value of r=0.856 and p=0.000. This shows that decreased serum IgE levels are significantly associated with decreased serum Periostin levels. The strength of this strong relationship indicates that changes in one variable tend to be followed by comparable changes in the other variable. This finding is consistent with a previous study by Oishi *et al*. which showed that there was a positive correlation between serum Periostin levels

and several other type 2 inflammatory biomarkers, including total IgE, in COPD patients. Their study found that increased periostin levels were often followed by increased serum IgE levels, reflecting that Type 2 inflammation plays an important role in the pathogenesis of COPD. These findings suggest that inflammatory mechanisms involving IL-4 and IL-13, which increase periostin and IgE production by B cells, play a role in airway inflammation and remodeling[7].

This study found that there was a moderate negative correlation between Serum Periostin Decrease and Length of Stay ($r = -0.592$, $p = 0.002$). This indicates that the higher the Serum Periostin Decrease, the shorter the duration of hospitalization. The moderate strength of this relationship suggests that changes in Serum Periostin correlate with changes in the duration of hospitalization. The reduction in LOS in the PR group and the SWD group, suggests that pulmonary rehabilitation programs can significantly reduce the duration of hospitalization. The study by Myers *et al*. examined the effect of pulmonary rehabilitation on readmission rates and LOS in COPD patients hospitalized for acute exacerbation of COPD. Their results showed that patients who received at least one pulmonary rehabilitation session after hospital discharge had a lower 30-day readmission risk and shorter LOS compared to patients who did not receive pulmonary rehabilitation. The study also found that pulmonary rehabilitation was associated with improved long-term outcomes and reduced healthcare burden. Their findings suggest that timely and effective rehabilitation interventions have a more direct and significant positive impact on hospitalization duration than biomarker measurements such as serum periostin, which is in line with this study[6].

The results of this study showed a moderate negative correlation between decreased serum IgE levels and Length of Stay (LOS) in COPD patients who experienced acute exacerbations, with a correlation value of $r=-0.591$ and $p=0.002$. This means that the higher the decrease in serum IgE levels, the shorter the duration of hospitalization. This finding is consistent with a study by Xie *et al*. who also found that patients with higher serum IgE levels had a shorter duration of hospitalization. This relationship suggests that increased serum IgE is associated with decreased duration of hospitalization, indicating that IgE may be an important biomarker in predicting clinical outcomes in patients with ECOPD[11]. The findings of this study are also consistent with a study conducted by Lommatzsch *et al*. They found that high total serum IgE levels correlated with an increased risk of exacerbations and decreased lung function, which may affect the duration of hospitalization. This relationship suggests that elevated serum IgE levels are associated with worse clinical conditions and increased LOS, so decreasing serum IgE levels may contribute to faster recovery and shorter duration of hospitalization. Thus, serum IgE may serve as an important biomarker in predicting clinical outcomes and aid in therapeutic decision-making to reduce LOS in COPD patients[5].

5. Limitations

Our limitation includes subjects who were not distinguish between subjects based on the cause and severity of COPD exacerbation, and we did not use double-blind randomization. There were variations in individual responses to the interventions, and these differences were not categorized according to the severity of the COPD exacerbation.

6. Conclusion

Combining pharmacological treatments with non-pharmacological interventions, such as pulmonary rehabilitation and early SWD therapy, significantly reduces inflammation markers (serum IgE and serum Periostin) and shortens the Length of Stay (LOS) for COPD exacerbation inpatients. These findings highlight a very potential for non-pharmacological interventions to significantly improve patient outcomes and we hope can reduce healthcare burdens. We recommend future research with larger population studies and longer intervention durations to confirm our findings and further explore these interventions benefits.

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