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Correlation of Serum IL-6 Levels with Muscle Mass, Muscle Strength, and Physical Performance in Elderly Gymnastics Community in Mohammad Hoesin General Hospital Palembang

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ABSTRACT

Background: Old age is related to geriatric syndrome where there are several health problems that often occur related to a decrease in body function and an increase in the inflammatory process. Decrease in muscle mass, muscle strength and physical performance will cause a condition of sarcopenia and frailty syndrome in the elderly. The importance of prevention so that sarcopenia does not occur in the elderly by evaluating the factors that can cause it, one of which is controlling interleukin 6 (IL-6) as proinflammatory. The purpose of this study was to determine the correlation between serum IL-6 levels with muscle mass, muscle strength and physical performance in the elderly gymnastics-community in Mohammad Hoesin General Hospital, Palembang. **Methods:** This research is an observational analytic study with a cross-sectional approach which was conducted at the Integrated Geriatric Clinic Internal Medicine RSMH Palembang from November 2019 to November 2020. A sample of 31 people aged > 60 years was examined for muscle mass, muscle strength, physical performance and IL-levels. 6 serum. All data processing and analysis in this study used the SPSS version 25 for Windows program. **Results:** of the 31 subjects, 27 were female (87.1%) and 4 male (12.9%). The mean value of muscle mass is 37.9 kg/m², muscle strength 23 kg, and physical performance 6.1 m/sec. There were 28 (90.3%) samples with elevated serum IL-6 levels, while 3 (9.7%) samples had normal levels. There was a significant negative correlation ($p = 0.000$) with a strong correlation strength ($r = -0.722$) between serum IL-6 levels and muscle mass and a significant negative correlation ($p = 0.050$) with a weak correlation strength ($r = -0.354$) between IL levels -6 serums with physical performance. **Conclusions:** There was a significant negative correlation between serum IL-6 levels and muscle mass and physical performance. So, it is very important to prevent an increase in serum IL-6 levels so that the elderly do not fall into a state of sarcopenia.

1. Introduction

The results of national development have created better social conditions in society and an increasing life expectancy, so that the number of elderly people (aged) is increasing. According to the world population aging 2019, the elderly population is increasing.¹

The Indonesian Ministry of Health stated that Indonesia had begun to enter a period of aging population, where there was an increase in life expectancy followed by an increase in the number of elderly people. Indonesia has experienced an increase in the number of old people from 18 million (7.56%) in

2010, to 25.9 million (9.7%) in 2019, and it is estimated that it will continue to increase in 2035 to 48.2 million people. (15.77%)²

Govinda (PERGEMI, 2015) stated that Old age is not a disease but an advanced stage of a life process characterized by a decrease in the body's ability to adapt to environmental stress.³

Old age is related to geriatric syndrome where there are several health problems that often occur, these signs indicate a decline in body function in old age which is the impact of lifestyle and previous disease history. Signs of geriatric syndrome include decreased

muscle function, muscle mass, bone mass, osteoporosis, easy falls, weight loss, dementia, lack of sleep, bladder disorders, delirium, decreased organ function and immunity.

The initial methods used to detect decreased muscle mass, bone mass and muscle function were tomography and MRI (including using anthropometric measurements), then developed by examinations using other methods such as ultrasound, bioimpedance analysis and dual-energy X-ray absorptiometry to calculate regionally the total muscle mass in the body. Evaluation of sarcopenia and illustrations related to old age can be seen through signs of decreased muscle mass, muscle function, physical performance

One of the strategies that can be achieved to prevent and reduce and delay the decline in musculoskeletal function in the elderly can be done through repair of inflammatory factors, because it can inhibit muscle protein synthesis, accelerate protein decomposition and increase the expression of protein inhibitor of muscle growth factor (myostatin) and muscle atrophy. In addition, the reduction in muscle mass also occurs due to high levels of IL-6 which can inhibit IGF-1, an anabolic hormone which is important for the formation of muscle tissue. As you get older, the production of cytokines increases, so that IL-6 levels also increase, making elderly people very at risk of sarcopenia.

Recent studies have shown a strong negative correlation between serum IL-6 levels and skeletal muscle mass. Consistently Tuttle et al (2020) also showed that there is a decrease in muscle mass and strength in the elderly with an increase in serum IL-6 levels

Based on the background of this problem, the researcher wanted to know the correlation between serum IL-6 levels with muscle mass, muscle strength, and physical performance in the elderly gymnastics-community at RSMH Palembang.

2. Methods

This study used an observational analytic design with a cross sectional approach. The research was conducted in the elderly gymnastics-community at

RSMH Palembang starting November 2019 until the number of samples was met.

The target population in this study were all elderly patients in the elderly gymnastics-community at RSMH Palembang. The affordable population is all samples aged ≥ 60 years who are members of the elderly gymnastics-community at RSMH Palembang. The research subjects were affordable populations who met the inclusion criteria. The exclusion criteria were: Subjects with acute conditions or illnesses, Subjects experiencing autoimmune diseases, Subjects with severe liver or kidney problems, Subjects with malignant diseases

All patients who met the sample inclusion and exclusion criteria and were willing to take part in the study by signing a consent form, then Identification, including: name, age, gender, education and occupation. Anamnesis (autoanamnesis / alloanamnesis) which includes: main complaints, additional complaints, history of disease, and drugs that have been used, history of chronic disease, history of smoking. The history was carried out by the researcher.

Physical examination includes height, weight, body mass index, vital sign, Body Impedances Analysis (BIA): BMI, fat mass (FM), free fat mass (FMM), Visceral Fat Analysis (VFA): Waist Circumference (WC) Skeleton Muscle Index (SMI) by researchers. Examination of serum IL-6 levels, blood draw is done after 1 hour of doing exercise. Measured by immunochemical quantification using the high-performance liquid chromatography method carried out at the Prodia Laboratory.

3. Results

The population of this study were 31 people who met the inclusion criteria, then all of them were measured muscle mass, walking time within 6 meters and hand grip strength. The Shapiro-Wilk normality test was carried out to see the distribution of data on the characteristics of research subjects. In data with normal distribution, the size of centering uses the mean / mean with the size of the spread using the

standard deviation (SB), while in data with an abnormal distribution, the size of centering uses the median and the size of the spread with a range of minimum and maximum values.

Judging from the general characteristics of the research sample in Table 1. The sample was dominated by women as many as 27 (87.1%) of the sample, while men were only 4 (12.9%) of the sample, with a mean age of 65 years, the youngest age 61 years and the oldest age 80 years. Samples aged <65 years were slightly more many 19 (61.3%) samples, while those aged ≥ 65 years 12 (38.7%) samples. In this study, the sample was dominated by a BMI value less than 14 (45.1%) and a BMI value over 13 (41.9%) with a mean BMI value of 22.05 ± 3.4 kg/m².

The mean value of muscle mass was 37.9 kg with the lowest muscle mass was 32.2 kg and the highest was 54.3 kg. Muscle strength has a mean value of 23 kg with the lowest muscle strength 16 kg and the highest 37 kg. Physical performance has a mean value of 6.1 m/s with the fastest running is 4.1 m/s and the longest is 11.5 m/s. Serum IL-6 levels had a mean value of 50 pg/mL with the lowest value 2.4 pg/mL and the highest 50 pg/mL. The sample of this study was dominated by serum IL-6 levels which increased by 28 (90.3%).

Table 2 showed that serum IL-6 levels in the elderly, elderly people aged 60-64 years there were 18 (64.3%) samples whose serum IL-6 levels increased by a median of 50 pg/mL, while at age ≥ 65 years there were 10 (35.7%) samples with a median of 50 pg/mL, the lowest serum IL-6 level was 42.8 pg/mL and the highest was 50 pg/mL.

Table 3. The results of the analysis using the Mann Whitney test showed that there was a significant correlation between serum IL-6 levels and muscle mass ($p = 0.038$) where the mean value of muscle mass and IL-6 level the increased serum was 38.5 kg, the lowest

was 32.2 kg and the highest was 54.3 kg. Meanwhile, muscle strength had a mean value of 23 kg, the lowest was 16 kg and the highest was 37 kg and the physical performance had a mean value of 6.05 m/s with the lowest was 4.1 m/s and the highest was 11.5 m/s

Table 4. where the results of the Spearman's rho correlation test showed a significant negative correlation with moderate strength correlation between serum IL-6 levels and muscle mass. The graph of the correlation between serum IL-6 levels and muscle mass can be seen in Figure 1.

Test results Multivariate linear regression analysis on muscle mass showed a significant negative correlation with a strong correlation between serum IL-6 levels and muscle mass. Meanwhile, muscle mass with BMI showed a significant negative correlation with moderate correlation strength. Can be seen in table 5.

Table 6. where the results of the Spearman's rho correlation test did not show a significant correlation between serum IL-6 levels and muscle strength. The graph of the correlation between serum IL-6 levels and muscle strength can be seen in Figure 2.

Test results Multivariate linear regression analysis on muscle strength showed a significant negative correlation with moderate strength correlation between muscle strength and gender and a significant negative correlation with very weak correlation strength between muscle strength and age. Can be seen in table 7.

In table 8. where the Spearman's rho correlation test did not show a significant correlation between serum IL-6 levels and physical performance. The graph of the correlation between serum IL-6 levels and physical performance can be seen in Figure 3

Test results Multivariate linear regression analysis on physical performance showed a significant negative correlation with a weak correlation between physical performance and serum IL-6 levels. Can be seen in table 9

Table 1. Characteristics of the research sample

	n (%)	Median (min-max)	Mean ± SD
Gender			
Man	4 (12.9%)		
Women	27 (87.1%)		
Age (years)		65 (61 - 80)	
< 65 years	19 (61.3)		
≥ 65 years	12 (38.7%)		
BMI			
Normal	4 (12.9 %)		22.05 ± 3.4
Less	14 (45.1%)		
More	13 (41.9%)		
Muscle mass (kg)		37.9 (32.2-54.3)	
Muscle strength (kg)		23 (16-37)	
Physical Performance (m/s)		6.1 (4.1-11.5)	
Levels of IL-6(pg/mL)			
Normal	3 (9.7%)		
To increase	28 (90.3%)		

Table 2. Serum IL-6 levels in the elderly

Serum IL-6 levels	< 65 years		≥ 65 years		P
	N (%)	Median (min-max)	N (%)	Median (min-max)	
Increasing	18 (64.3%)	50 (50-50)	10 (35.7%)	50 (42.8-50)	0.328 ^a
Normal	1 (33.3%)	2.4 (2.4-2.4)	2 (66.7%)	3.9 (3.9-3.9)	0.144 ^b

a chi-square test, b mann whitney test, p value is significant if p<0.05

Table 3. Distribution of IL-6 serum levels, muscle mass, muscle strength, and physical performance

	Serum IL-6 levels		p
	Increasing	Normal	
Muscle mass (kg)	38.5 (32.2-54.3)	33.2 (32.7-34)	0.038
Muscle strength (kg)	23 (16-37)	21 (19-30)	0.401
Physical performance (m/s)	6.05 (4.1-11.5)	7.4(5.5-10)	0.348

The Mann Whitney test p value was significant if p <0.05

Table 4. Correlation of serum IL-6 levels with muscle mass

	Serum IL-6 level	
	R	P
Muscle mass	-0.577	0.032

Spearman's rho correlation test, p value is significant if p <0.05. The strength of correlation is very weak if r <0.2, weak if r = 0.21-0.4, moderate if r = 0.41-0.6, strong if r = 0.61-0.8 and very strong if r > 0.8

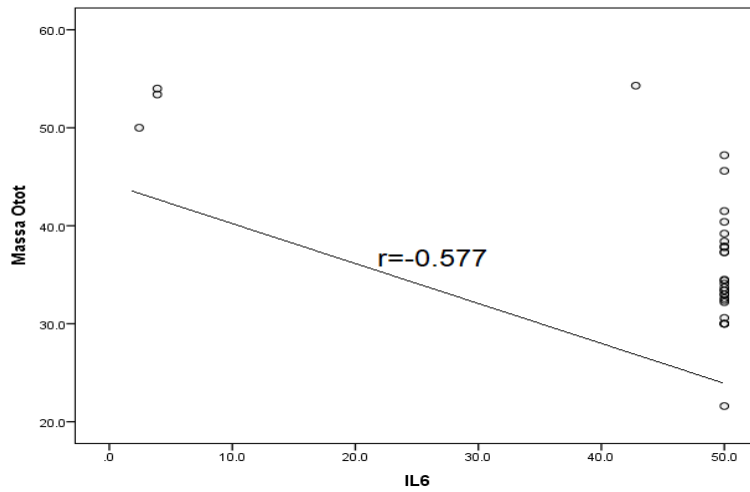


Figure 1. Correlation of serum IL-6 levels with muscle mass

Table 5. Multivariate analysis of muscle mass linear regression

Model	Unstandardized coefficients		Standardized coefficients	Sig.	r
	B	Std. error	Beta		
3 (Constant)	70.662	7.409		.000	
Body mass index	-711	.292	-.307	.021	-0.418
IL-6	-393	.071	-.696	.000	-0.722

Multivariate linear regression test, p value is significant if $p < 0.1$, the strength of the correlation is very weak if $r < 0.2$, weak if $r = 0.21-0.4$, moderate if $r = 0.41-0.6$, strong if $r = 0.61-0.8$ and very strong if $r > 0.8$

Table 6. Correlation of IL-6 Serum Levels with Muscle Strength

	Serum IL-6	
	r	p
Muscle strength	0.288	0.116

Spearman's rho correlation test, p value is significant if $p < 0.05$. The strength of correlation is very weak if $r < 0.2$, weak if $r = 0.21-0.4$, moderate if $r = 0.41-0.6$, strong if $r = 0.61-0.8$ and very strong if $r > 0.8$

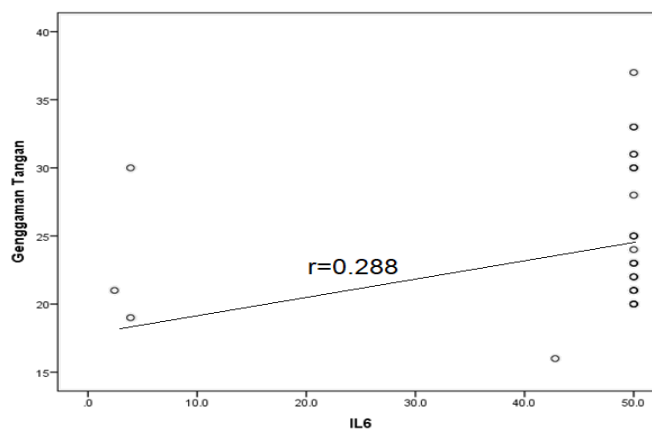


Figure 2. Correlation of IL-6 serum levels with muscle strength

Table 7. Multivariate linear regression analysis of muscle strength

Model		Unstandardized coefficients		Standardized coefficients	Sig.	r
		B	Std. error	Beta		
3	(Constant)	47.478	15.262		.004	
	Gender	-7.763	2.498	-.516	.004	-.506
	Age	-.124	.207	-.100	.052	-.113

Multivariate linear regression test, p value is significant if $p < 0.1$, the strength of the correlation is very weak if $r < 0.2$, weak if $r = 0.21-0.4$, moderate if $r = 0.41-0.6$, strong if $r = 0.61-0.8$ and very strong if $r > 0.8$

Table 8. Correlation of IL-6 serum levels with physical performance

Physical performance	Serum IL-6	
	r	p
	-0.249	0.176

Spearman's rho correlation test, p value is significant if $p < 0.05$. The strength of correlation is very weak if $r < 0.2$, weak if $r = 0.21-0.4$, moderate if $r = 0.41-0.6$, strong if $r = 0.61-0.8$ and very strong if $r > 0.8$

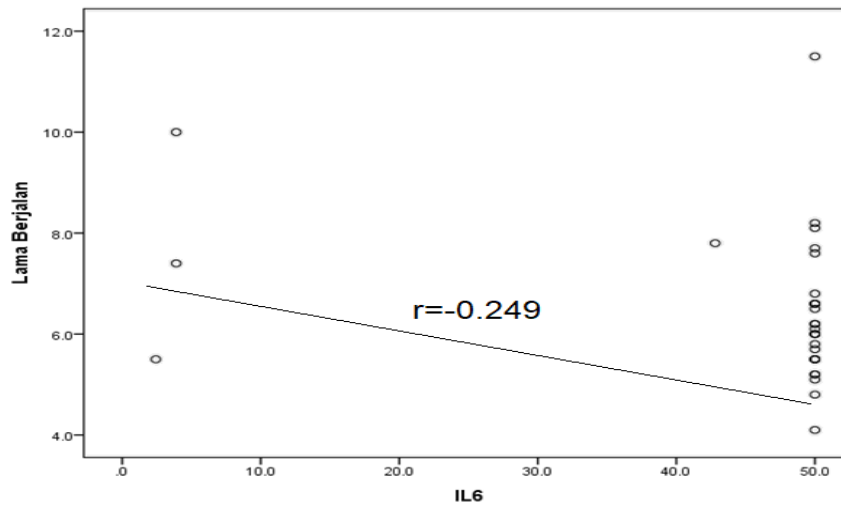


Figure 3. Correlation of IL-6 serum levels with physical performance

Table 9. Multivariate analysis of physical performance linear regression

Model		Unstandardized coefficients		Standardized coefficients	Sig.	r
		B	Std. error	Beta		
4	(Constant)	2.125	4.231		.000	
	IL-6	.131	.064	-.354	.050	-.354

4. Discussion

In this study, the distribution of serum IL-6 levels, muscle mass, muscle strength and physical performance can be seen in table 3. The results of the analysis using the Mann Whitney test showed that

there was a significant correlation between serum IL-6 levels and muscle mass ($p = 0.038$) where the mean value of muscle mass with serum IL-6 levels increased by 38.5 kg, the lowest was 32.2 kg and the highest was 54.3 kg. Meanwhile, muscle strength has a mean value

of 23 kg, the lowest is 16 kg and the highest is 37 kg and physical performance has an average value of 6.05 m / s with the fastest walking is 4.1 m / s and the longest is 11.5 m/s.

Tournadre et al's 2019 study found that there were differences in serum IL-6 levels in 6 healthy elderly and 15 elderly with arthritis, where the mean muscle mass value in the elderly group with arthritis was 17.7 ± 5.4 kg while in the healthy group 20.1 ± 3.9 kg, but Tournadre et al also found that muscle strength (30.5 ± 5.9 kg in the arthritis group) and physical performance were normal, the results of the Mann Whitney test showed a significant relationship between IL-6 levels. serum with muscle mass in the elderly.¹¹ Consistent with this study, Dutra et al 2015 also reported that there was a significant correlation between increased serum IL-6 levels with age, fat mass, muscle mass, and muscle strength.¹² Crescioli et al in 2020 also found that there was a significant negative correlation between serum IL-6 levels and age muscle mass and physical performance.¹³

Activation of inflammatory pathways due to age and due to various diseases, that commonly accompany aging, is an important contributor to the occurrence of sarcopenia.⁵ Bano et al. (2017) in their meta-analysis study reported a correlation between serum IL-6 levels and muscle strength.¹⁴ Bian et al (2017) also reported higher serum TNF- α and IL-6 levels in people > 60 years with sarcopenia compared to those who did not.⁶ Reduction in muscle mass is thought to result from the influence of chronic inflammatory cytokines on the population of muscle satellite cells that are stem cells or precursors that will develop into myoblast cells and muscle fibers. Chronic disease is the most common cause of activating the inflammatory pathway.¹⁵

This study found a significant negative correlation with strong correlation between serum IL-6 levels and muscle mass. Consistent with this research, the meta-analysis study conducted by Tuttle et al. In 2020 also concluded that there was a significant negative correlation between serum IL-6 levels and muscle mass.¹⁰ Da Cunha Naschimento, Dahan et al in 2018 also found a significant negative correlation between IL-

6 levels serum with muscle mass and concluded that the more serum IL-6 levels are, the muscle mass will decrease

Yakabe et al in 2018 reported a linear reduction in muscle mass and skeletal muscle strength where at the time of entering the age of 80 there was a reduction in muscle mass by 50% .¹⁷ According to Bian et al in 2017, the impact on daily activities and health status due to sarcopenia, looks more severe at a later age and can also be a part of frailty syndrome. Sarcopenia is also associated with acute and chronic diseases, increased insulin resistance, fatigue, frequent falls and death among the elderly.⁶ Koltover et al in 2019, lack of muscle mass is also associated with the incidence of joint-muscle disorders, especially rheumatoid arthritis in women.¹⁸

The correlation of serum IL-6 levels with muscle strength can be seen in Table 6. and 7 where the results of the Spearman's rho correlation test and multivariate analysis did not show a significant correlation between serum IL-6 levels and muscle strength. Consistent with this study, Tournadre et al also did not find a significant correlation between serum IL-6 levels and muscle strength.¹¹ This may be due to insufficient samples. In contrast to Da Cunha Naschimento's research, Dahan et al in 2018 examined serum IL-6 levels in obese elderly and found a significant negative correlation between serum IL-6 levels and muscle strength.

Wilson et al 2017 concluded that data on inflammatory cytokines especially IL-6 and the occurrence of sarcopenia were limited and inconsistent. IL-6 is thought to play a dual role in the development of sarcopenia and decreased muscle strength.¹⁵ Livshits et al in 2019 revealed that it was initially thought that this IL-6 cytokine is produced only by immune cells, while other findings also identified muscle cells as producers of IL-6. In fact, muscle is a major source of circulating IL-6, especially in response to exercise.^{15,19}

Nelke C et al in 2019 concluded, IL-6 can provide pro-inflammatory and anti-inflammatory effects and even increase muscle anabolism or catabolism depending on the target structure, dominant cytokine

environment and mode of release. IL-6 is insufficient to induce muscle wasting, depends on synergistic interactions with other factors that mediate the inflammatory response, depends on chronic exposure to IL-6 and the concomitant activity of other proinflammatory cytokines such as TNF α . Contra circulating IL-6 concentrations increased drastically after exercise and were dependent on the intensity of muscle training suggesting that IL-6 was released from skeletal muscle to restore muscle homeostasis after exercise. IL-6 signaling is essential for skeletal muscle regeneration and hypertrophy by regulating satellite cell function and enhancing glucose metabolism. Exercise leads to Ca²⁺ release from the sarcoplasmic reticulum. In response to Ca²⁺, calcineurin activator of activated T-cell nucleus factor mediates IL-6 production in monocytes. Increased Ca²⁺ inhibits TNF α . As a result, in response to exercise only IL-6 was secreted, whereas TNF α has remained largely unchanged. Only vigorous exercise like running a marathon triggers TNF α .²⁰ Changes in muscle strength due to age can be affected by the number and size of muscles that change to atrophy and hypoplasia, decrease in slow and fast motor units and the presence of atrophy in type I and II muscle fibers. Type II muscle fibers are fast fibers that have higher glycolytic potential, low oxidative capacity and faster response than type I (slow fibers). There is a conversion from type II to type I fibers because of the potential adaptive response. In elderly muscles, the decrease in type I and II fibers results in changes in muscle function, especially muscle strength

The correlation of serum IL-6 levels with physical performance can be seen in Table 8. where the Spearman's rho correlation test did not show a significant correlation between serum IL-6 levels and physical performance. However, the multivariate analysis shows a significant negative correlation with the strength of the weak correlation. Consistent with this study, Rachim et al. In 2020 found that there was a significant negative correlation between serum IL-6 levels and physical performance.²¹ Longitudinal research by Wanigatungabano et al in 2019 found that

there was a significant negative correlation between serum IL-6 levels and physical performance.²² So it can be concluded that the increase in serum IL-6 levels will further reduce physical performance.

5. Conclusions

There is a significant negative correlation with the strength of a strong correlation between serum IL-6 levels and muscle mass and a significant negative correlation with the strength of a weak correlation between serum IL-6 levels and physical performance in the elderly gymnastics-community at RSMH Palembang. There is no correlation between serum IL-6 levels and muscle strength in the elderly gymnastics-community at RSMH Palembang.

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