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## Correlation of Cardiorespiratory Fitness with Fatigue Severity Scale (FSS) on Systemic Lupus Erythematosus (SLE) Patients at RSUP Dr. Hasan Sadikin Bandung

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### ABSTRACT

**Background** Systemic Lupus Erythematosus (SLE) is a multifactorial and heterogenous systemic autoimmune disease, involving multisystem organ and marked with the production of autoantibodies. SLE has general constitutional symptom such as fatigue and usually is the main symptom causing limited functional condition on patients. Assessment for cardiorespiratory fitness can be done with various methods, one of them measuring Metabolic Equivalents (METs). The purpose of this study was to examine the correlation between cardiorespiratory fitness and Fatigue Severity Scale (FSS). **Methods** The sampling method used was the total sampling method. Out-patients diagnosed with SLE were screened via medical records according to inclusion and exclusion criteria. SLE patients filled an Indonesian version of the FSS questionnaire sheet and did the six-minute walk test based on standard protocol on a 30-meter track. The total distance patients had crossed was turned into  $VO_2$  max with Nury equation, then turned again into cardiorespiratory fitness with METs unit. A correlation analysis between cardiorespiratory fitness and FSS was done next. **Results** There were 28 patients participating in this research. Correlation analysis resulted in a negative correlation with no statistical meaning between cardiorespiratory fitness and FSS ( $r = -0,27$ ;  $p > 0,05$ ). **Conclusion** There is no correlation between cardiorespiratory fitness and FSS in SLE patients.

### 1. Introduction

Systemic Lupus Erythematosus (SLE) is a multifactorial and heterogenous systemic autoimmune disease, involving multisystem organ

and marked with the production of autoantibodies.<sup>1</sup> SLE can affect all organs in a human body.<sup>2</sup> Fatigue is the most common constitutional symptom

(80%) of SLE, usually the main symptom causing limited functional condition on patients.<sup>1,3</sup> Grace E. Ahn and Rosalind Ramsey-Goldman in their research in 2012 showed that SLE patients had higher fatigue level than the healthy population.<sup>4</sup> This condition can downgrade the intensity and the frequency of daily physical activities, worsening patients' disability state.<sup>3</sup> Patient with unmet World Health Organization (WHO) recommendation for physical activities tends to have higher disease progressivity.<sup>5</sup>

SLE patients have lower aerobic fitness and exercise capacity level than control population; this physical disability corresponds to the high level of fatigue.<sup>6</sup> Sandor Balsamo and Leopoldo dos Santos-Neto's research in 2011 also pointed that SLE patients had lower cardiorespiratory capacity compared to healthy subjects.<sup>7</sup> Initiation of physical activities and the decrease in sedentary time are important to be done because they can help reduce fatigue level.<sup>5,8,9</sup> Until recently, treatments for SLE have not been optimal, making it important for patients, their surroundings, and medical personnel to understand the SLE patients' cardiorespiratory status and its correlation with fatigue level as the basic of promotive preventive act.<sup>10</sup>

Many studies examine cardiorespiratory fitness with Metabolic Equivalents (METs) measurement and the maximum O<sub>2</sub> volume (VO<sub>2 max</sub>) using direct method.<sup>11</sup> This direct measurement requires several conditions such as specialized tools and qualified examiners, making it difficult

to be conducted in general setting, thus a field test like the six-minute walk test can be an alternative choice.<sup>12</sup> The six-minute walk test has been widely use in various studies to assess the quality of patients' life and cardiorespiratory fitness on SLE patients and other disease alike. In the global scale, there has been a comparative study about the result of the six-minute walk test and the quality of life on pre-menopause SLE patients compared to the control population; SLE patients ambulated shorter distance compared to control population and can be associated with worse quality of life.<sup>13</sup> Research done by Colin Tech *et al.* in 2002 studying aerobic fitness, muscle strength, and physical disabilities in SLE patients using treadmill-walking test indicated that physical disabilities could be determined from aerobic fitness and related with fatigue. There has been no study published about the correlation between cardiorespiratory fitness and the six-minute walk test with fatigue level on SLE patients in Indonesia and overseas.

Research about the correlation of cardiorespiratory fitness with fatigue level in SLE patients is expected to be able to give clinicians, the public, and especially SLE patients themselves informations on the importance of prevention, detection, and early intervention on cardiorespiratory alteration signs along with the importance of routine measurable physical activities. This research is also hoped to be able to motivate SLE patients in increasing daily activities to counter fatigue, as well as to become one of the base theory for clinicians to suggest physical exercise regimes for SLE patients.

## **Methods**

This study used cross sectional study design. The data was taken with the Indonesian version of Fatigue Severity Scale (FSS) questionnaire to determine the fatigue level and the six-minute walk test were done to determine the cardiorespiratory fitness on out-patients diagnosed with SLE coming to control at the Rheumatology Polyclinic, Departement of Internal Medicine, dr. Hasan Sadikin General Hospital from September to October 2019, followed with a correlation test.

Inclusion criteria were those ranging from 18 to 50 years old, having normal Body Mass Index (BMI) ( $18,5-24,9 \text{ kg/m}^2$ )<sup>14</sup>, newest MEX-SLEDAI score  $\leq 5$ , and the ability to walk independently both by themselves or with assisting walking aids such as a walking cane. Exclusion criteria were the presence of absolute contraindications from the six-minute walk test such as unstable angina and myocardium infarction a month before, the existence of relative contraindications from the six-minute walk test such resting heart rate more than 120, systolic blood pressure  $>180 \text{ mmHg}$ , and diastolic blood pressure  $>100 \text{ mmHg}$ <sup>15</sup>, and having musculoskeletal, respiratory, cardiopulmonal, or other systemic diseases which are not related to SLE.

The study was done after gaining ethical approval number 872/UN6.KEP/EC/2019 by Ethical Committee of Faculty of Medicine, Universitas Padjadjaran and research permit number LB.02.01/X.2.2.1/13594/2019 by dr. Hasan Sadikin General Hospital Bandung.

Sampling method used was the total sampling method, in which all population meeting the research criteria was used as samples. Minimum sum of

samples was calculated using correlative analysis' minimum sum of samples equation with  $Z_\alpha = 5\%$  and  $Z_\beta = 10\%$ . In this study,  $r$  value had not been determined yet because there was no reference found from previous literature study, resulting in conducting a preliminary study on the first ten patients to find the  $r$  value. Based on the preliminary study, the value found was  $r = -0.70$ , thus the minimum sum of samples were 19 patients.

First, screening on out-patients diagnosed with SLE coming to control at the Internal Medicine section of the Rheumatology Polyclinic dr. Hasan Sadikin General Hospital Bandung was done through medical records based on inclusion and exclusion criteria. Clinical manifestation at the time of SLE diagnosis data collecting was obtained from Hasan Sadikin Lupus Registry by the Rheumatology Division of the Department of Internal Medicine dr. Hasan Sadikin General Hospital Bandung. The data were classified based on SLE diagnosis criteria from the American College of Rheumatology (ACR).<sup>16</sup> SLE patients willing to participate in this research and had filled the infomed consent sheet then filled the Indonesian version of the Fatigue Severity Scale (FSS) questionnaire sheet which had the validity and reliability test done before.<sup>17</sup> SLE patients then did the six-minutes walk test on the same day according to the standard procedure from ATS Statement: Guidelines for the Six-Minute Walk Test from American Thoracic Society (ATS) on a 30-meter track.<sup>15</sup> Total distance ambulated by patients was turned into  $\text{VO}_2$  max with Nury equation<sup>18</sup>, then the calculation resut was turned again into cardiorespiratory fitness with METs unit based on Adult Compendium of

Physical Activities in 2011.<sup>19</sup>

Data collected were analyzed with statistical software IBM SPSS Statistics version 25.0. Data analysis of the correlation between cardiorespiratory fitness and FSS was done using Pearson correlation.

## Result

Until the end of the study period, there were 28 cardiorespiratory fitness and FSS data obtained from SLE patients meeting the criteria. Subject demography data for this research were

represented in Table 1. All 28 patients (100%) of this research were females. The mean of patients' age was 30 years old, with mean height 155,64 centimeters and mean weight 53,07 kilograms. The most common clinical manifestation according to diagnosis criteria from the American College of Rheumatology (ACR) were positive Antinuclear Antibody (ANA) test (28 patients; 100%), arthritis (24 patients; 85,7%), and hematological and immunological abnormality each numbering 16 patients (57,1%).

**Table 1 Demographic data of Systemic Lupus Erythematosus (SLE) patients**

Research Variables	SLE Patients (n=28)
Age (years) <sup>a</sup>	30,04 (8,81)
Height (cm) <sup>a</sup>	155,64 (7,10)
Weight (kg) <sup>a</sup>	53,07 (7,71)
Biological Sex <sup>b</sup>	
• Male	0 (0%)
• Female	28 (100%)
Clinical manifestations at the time of SLE diagnosis <sup>b</sup>	
• Malar rash	14 (50%)
• Discoid rash	9 (32,1%)
• Photosensitivity	10 (35,7%)
• Oral ulcer	10 (35,7%)
• Arthritis	24 (85,7%)
• Serositis	4 (14,3%)
• Renal abnormality	16 (57,1%)
• Neurological abnormality	5 (17,9%)
• Hematological abnormality	16 (57,1%)
• Immunological abnormality	9 (32,1%)
• Antinuclear Antibody (ANA)	28 (100%)

<sup>a</sup>Mean(SD)/ <sup>b</sup>Sum(Percentage)/ <sup>c</sup>Median (Minimum-Maximum)

Details: 1 patient might have >1 manifestation

**Table 2. FSS and cardiorespiratory fitness data from SLE patients**

Research Variables	SLE Patients (n=28)
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### Fatigue Severity Scale Score

• Statement 1 <sup>a</sup>	4 (1-7)
• Statement 2 <sup>b</sup>	4,18 (1,70)
• Statement 3 <sup>b</sup>	3,86 (1,72)
• Statement 4 <sup>a</sup>	4 (1-7)
• Statement 5 <sup>b</sup>	3,96 (1,77)
• Statement 6 <sup>a</sup>	5 (1-7)
• Statement 7 <sup>a</sup>	4 (1-7)
• Statement 8 <sup>b</sup>	4,11 (1,73)
• Statement 9 <sup>a</sup>	4 (1-7)

**Six-minute walk test distance (m)<sup>b</sup>** 394,88 (65,88)

**VO<sub>2</sub> max (mL/kg/minute)<sup>b</sup>** 13,35 (3,74)

<sup>a</sup>Median (Minimum-Maximum)/<sup>b</sup>Mean(SD)

**Table 3. Correlation coefficient between cardiorespiratory fitness and Fatigue Severity Scale (FSS)**

Research Variables	SLE Patients (n=28)	r (p)
<b>Cardiorespiratory fitness (METs)<sup>a</sup></b>	3,81 (1,07)	-0,27 (0,16)
<b>Fatigue Severity Scale score<sup>a</sup></b>	4,04 (1,50)	

SLE: Systemic Lupus Erythematosus

METs: Metabolic Equivalents

<sup>a</sup>Mean(SD)

## 4. Discussion

Median age of the study subjects was 30 years old with female being the dominant sex (100%). This matches with *Infodatin: Situasi Lupus di Indonesia* (Centers of Data and Information: Lupus Condition in Indonesia) published by Ministry of Health Indonesia in 2017 which stated that those in productive age group (15 to 50 years old) were prone to SLE.<sup>20</sup> The study done by Frances Rees *et al.* about the systematical review of SLE prevalence and incidence all around the globe pointed out that the peak incidence age of women is between 30 to 70 years old; meanwhile men is between 50 to 70 years old. The same study stated that women were more prone to SLE than men with ratio between 2:1 and 15:1.<sup>21</sup> Other research conducted by Lani Hamijoyo *et al.* at dr. Hasan Sadikin General Hospital Bandung indicated that

female was the dominant sex in the demography data of SLE patients.<sup>22</sup>

The most common clinical manifestation based on the diagnosis criteria from the American College of Rheumatology (ACR) were positive Antinuclear Antibody (ANA) test (28 patients; 100%), arthritis (24 patients; 85,7%), and hematological and immunological abnormality each numbering 16 patients (57,1%). This result slightly differs from another study done by Lani Hamijoyo *et al.* at dr. Hasan Sadikin General Hospital Bandung which denoted arthritis (75.5%), malar rash (68.3%), and photosensitivity (60.6%) with most patients having a positive ANA test (98.4%) as the most common clinical manifestation.<sup>22</sup>

FSS mean score of the study subjects was 4,04. A study conducted by Yuan Zhuang *et al.* in China examined FSS score

on SLE patients with cutoff score  $\geq 4$  to define fatigue in case and control, interpreting the higher the FSS score the more severe the fatigue.<sup>23</sup> This showed that fatigue was found in study subject. Grace E. Ahn and Rosalind Ramsey-Goldman in their research in the United States of America indicated that SLE patients had higher fatigue level than the healthy population.<sup>4</sup>

Many studies express cardiorespiratory fitness in the form of Metabolic Equivalents (METs).<sup>11</sup> The MET term based on Adult Compendium of Physical Activities in 2011 were the result of energy cost ( $\text{VO}_2$  mL/kg/minute) divided with 3,5 mL/kg/minute.<sup>19</sup> METs can be assessed from many tests chosen based on patients, conditions, and equipments and trained personnel available. The six-minute walk test is one the field test used to evaluate cardiorespiratory fitness.<sup>24</sup> Data analysis result showed the mean distance of the study subjects on the six-minute walk test was 394,88 meters. In a study done by Nur Nudwinuringtyas *et al.* examining the validity and reliability of the six-minute walk test on the 15-meters track at Universitas Indonesia, mean track distance of healthy patients obtained was 516,72 meters for female and 581,89 meters for male.<sup>25</sup> Another study at the same university by Fathia Arsyiana showed the mean distance of SLE patients on the six-minute walk test was 364,35 meters.<sup>26</sup> Study done by Sandor Balsamo *et al.* in Brazil stated that pre-menopause SLE women ambulated shorter mean distance (598 meter) compared to control population (642 meter).<sup>13</sup>

In this study, the mean  $\text{VO}_2$  max was 13,35 mL/kg/minute. Study at Universitas Negeri Surabaya by Wahyu Setyawan and Juanita Dolores H.N.,  $\text{VO}_2$  max in high school-level students examined with Multistage Fitness Test (MFT) was 33,29 mL/kg/minute.<sup>27</sup> Another study conducted by Revina Andayani *et al.* at Universitas

Muhammadiyah Surakarta showed mean  $\text{VO}_2$  max of college students who regularly exercised (71,55 mL/kg/minute) is higher than those who did not (57,12 mL/kg/minute).<sup>28</sup> A study done by Randall E. Keyser *et al.* at the United States of America measuring  $\text{VO}_2$  peak on female SLE patients (case) using treadmill showed lower result (20,1 mL/kg/minute) compared to that of control population (28,9 mL/kg/minute).<sup>29</sup>

Mean METs of the subjects was 3,81. According to O'Dwyer T *et al.*, SLE patients encounter more limitations in doing physical activity: arthritis, arthralgia and avascular necrosis, serositis, lungs involvement, fatigue, depression, and other comorbidities.<sup>9</sup> Research done by Sandor Balsamo *et al.* indicated that SLE patients had lower cardiorespiratory capacity and muscle strength compared to healthy subjects.<sup>7</sup>

Based on correlation analysis result, there was a negative correlation with no statistical meaning between cardiorespiratory fitness and FSS ( $r$  value = -0,27;  $p > 0,05$ ). In studies existed, fatigue in SLE patients might correspond with physical activity and would eventually reduce the intensity and frequency of daily physical activities.<sup>3,4</sup> Patients caught up in sedentary lifestyle appear more exhausted, further limiting daily physical activities and prolonging their sedentary time, thus experiencing in worse fatigue.<sup>5</sup> Sedentary lifestyle may worsen SLE symptoms which results in the decrease of functional capacity.<sup>3</sup> This is supported by a study showing SLE patients with lower cardiorespiratory capacity than healthy subjects.<sup>7</sup> In a study led by Benjamin Y. Tseng and Patricia Kluding researching patients with chronic stroke, a significant negative correlation between fatigue level and  $\text{VO}_2$  peak was obtained, although it did not correlate with the six-minute walk test.<sup>30</sup> Research conducted by Colin Tench *et al.* pointed out that SLE patients had

lower aerobic fitness and exercise capacity level than control population. This physical disability is related to the high level of fatigue, aerobic fitness, BMI, and depression.<sup>6</sup>

#### *Limitation*

The limitations of this study included several aspects. This study used FSS questionnaire which has 90% sensitivity and 84% specificity to measure Chronic Fatigue Syndrome (CFS). Further research can be done using fatigue questionnaire with the best sensitivity and specificity according to existing study, e.g. ME/CFS Fatigue Types Questionnaire (MFTQ) Post-Exertional Fatigue Scale which is the best scale with 95% sensitivity and 86%.<sup>31</sup>

Fatigue in SLE can be affected by physical activities, quality of sleep, obesity, emotional condition, deficiency/insufficiency of vitamin D, comorbidity, related to the SLE itself, or other medications used for SLE therapy. The study shows no significant difference between fatigue in patients with corticosteroid treatment, nonsteroidal anti-inflammatory drugs (NSAIDs), and psychotropic medication and those without.<sup>4</sup> Another study shows that pain, depression, and stress play a role in fatigue level in SLE patients, meanwhile disease activity, physical healthiness, and sleep have no correlation.<sup>32</sup> In a further study, the correlation of those factors with fatigue level can be assessed, resulting in a more accurate conclusion.

This study did not measure factors corresponding with fatigue level and cardiorespiratory fitness (six-minute walk test and VO<sub>2</sub> max). The six-minute walk test is influenced by a couple of determinants: age, sex, height, weight, Forced Expiratory Volume (FEV), and ethnics.<sup>34</sup> Further research can involve more thorough assessment via collecting and measuring on FEV and ethnics. Other factors affecting VO<sub>2</sub> max such as genetics, age, sex, physical activities, body fat, smoking

status, and medical conditions can also be considered for further research.<sup>35</sup> Physical activity has several measurement methods, including self-reporting questionnaires as the most commonly used, so that further study could consider physical activity assessment using the Indonesian version of questionnaires which have already had validity and reliability test.<sup>36</sup>

#### **Conclusion**

There is no correlation between cardiorespiratory fitness and FSS in SLE patients. Further study using the most accurate existing questionnaire of fatigue level and assessing factors which could affect the variables measured is recommended in order to achieve more accurate conclusion.

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