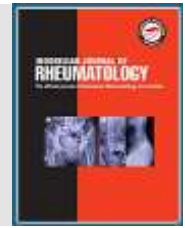




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Lupus Low Disease Activity State Associated with Lower Fatigue: A Preliminary Study

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ABSTRACT

Background Systemic Lupus Erythematosus (SLE) is an autoimmune disease with heterogeneous clinical manifestations including fatigue. Previous studies aimed at proving the relationship between fatigue and SLE disease activity showed conflicting results. In 2015, Asia Pacific Lupus Collaboration (APLC) developed low disease activity criteria, named Lupus Low Disease Activity State (LLDAS). Patients who spend more time in LLDAS have significantly lower morbidity. This study aimed to evaluate the association between disease activity based on LLDAS and fatigue. **Methods** This is an analytical cross-sectional study. Subjects were SLE patients at rheumatology clinic in Dr. Hasan Sadikin Hospital, Bandung during June-January 2018. Subjects were evaluated based on LLDAS criteria and divided into 2 groups: LLDAS and non-LLDAS. Fatigue status of the subjects was assessed with Fatigue Severity Scale (FSS). **Results** A hundred and thirty-three subjects were included in this study, divided into 63 subjects in LLDAS group and 60 subjects in non-LLDAS group. Nineteen subjects (30.2%) in LLDAS group had fatigue and 39 subjects (65%) in non-LLDAS had fatigue. There was a significant association between LLDAS and fatigue ($p < 0.001$). Nonetheless, fatigue level in LLDAS group was still high since disease activity was not the only factor related to fatigue. Fatigue may be a distinct clinical manifestation of neuropsychiatric lupus and may be independent of lupus disease activity. **Conclusions** There was a significant association between LLDAS and fatigue showed by lower fatigue level was found in the LLDAS group than in the non-LLDAS group.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by various clinical manifestations.¹⁻⁴ Clinical manifestations are vary among individuals, from minimally symptomatic to life-threatening condition.⁴⁻⁷ Fatigue is one of most

important manifestations of SLE and also affects physical, social, and emotional functioning. Most individuals with SLE reported fatigue to be most disabling symptom.⁸

Fatigue could be mediated from any physical

illness but also from social distress or depression. Fatigue can be measured subjectively by using a self-administered questionnaire. Fatigue Severity Scale (FSS) is a questionnaire, consists of 9 questions to determine fatigue severity subjectively. It is proven to have high validity and consistency, also in identifying fatigue in chronic disease adequately.⁹⁻¹¹

Objective clinical parameters are needed to monitor fluctuation of SLE disease activity. In 2015, Asia Pacific panel of SLE experts developed low disease activity criteria, named Lupus Low Disease Activity State (LLDAS). LLDAS is defined as a low disease activity state, which, if persists, is associated with a lower likelihood of poor outcome, considering disease activity and drug safety. Patients spends more time in LLDAS have significantly reduced morbidity due to organ damage.¹²

Previous studies aimed at proving the relationship between fatigue and SLE disease activity showed conflicting results. This study uses LLDAS criteria in determining SLE disease activity. The aim was to evaluate the association between disease activity based on LLDAS and fatigue.

2.Methods

Study Design

This is a analytical cross-sectional study. Subjects were SLE patients at Rheumatology Clinic Dr. Hasan Sadikin Hospital, Bandung in June –August 2017. This study has involved subjects of Asia Pacific Lupus Collaboration LLDAS Validation Study.

Inclusion criteria of this study were SLE patients who were 18 years old or older, were evaluated according to the *American College of Rheumatology* (ACR) 1997¹³ or *Systemic Lupus International Collaborating Clinics* (SLICC) 2012,¹⁴ also those who could read, write and understand the given informed consent. Exclusion criteria of this study were pregnant women, patient with poor medical state, or with psychiatric disturbance and uncooperative. Subjects were evaluated based on LLDAS criteria and divided into 2 groups: LLDAS and non-LLDAS.

Fatigue status of the subjects were assessed individually using FSS.

Ethics

The study was approved by The Health Research Ethics Committee, Dr. Hasan Sadikin Hospital Bandung.

Statistics

All collected data was analyzed using the SPSS v20.0. Categorical data was presented in frequency and percentage. Categorical analysis between fatigue and disease activity based on LLDAS were analyzed using Chi-squared test, while numerical analysis between FSS score and LLDAS were analyzed using independent T-test, considered as statistically significant if $P < 0.05$.

3.Results

Data collection was conducted during June – January 2018, at Rheumatology Clinic Dr. Hasan Sadikin Hospital, Bandung. A hundred and twenty-three patients who met the inclusion criteria were included in the study, divided into 63 subjects in LLDAS group and 60 subjects in non-LLDAS group.

Out of 123 patients, 118 (95.9%) were female. Patients from LLDAS group aged between 19-62 years old (median 35 years old) and non-LLDAS group aged 20-57 years old (median 32 years old). Both groups were matched for education and occupational status. Median duration of illness in LLDAS patients was longer than median duration of illness in non-LLDAS patients (median 6 years [1-30 years] vs 4 years ([1-19 years])). Baseline characteristics of study subjects were shown in Table 1.

Less than half subjects (30.2%) from LLDAS group had higher incidence of fatigue with mean FSS score 30.25 (SD 11.0), ranged from 9-59. Thirty-nine subjects (65.0%) from non-LLDAS group had significantly higher incidence of fatigue with mean FSS score 39.27 (SD 10.3), ranged from 18-62 (P value < 0.001). The non-LLDAS group had higher

incidence of fatigue than LLDAS group. Chi-square analysis revealed significant association ($p < 0.001$) between SLE disease activity based on LLDAS criteria and fatigue. (Table 2)

Table 1. Basic Characteristics

Variable	Non-LLDAS (n=60)	LLDAS (n=63)	p value
Age (Years), (median (min-max))	32 (20-57)	35 (19-62)	0.047 ^a
Sex, n (%)			
Male	2 (3.3)	3 (4.8)	0.523 ^b
Female	58 (96.7)	60 (95.2)	
Educational background, n (%)			
Elementary school	6 (10.0)	7 (11.1)	0.544 ^b
Junior high school	11 (18.3)	6 (9.5)	
Senior high school	29 (48.3)	38 (60.3)	
Diploma III	6 (10.0)	4 (6.3)	
Bachelor	8 (13.3)	8 (12.7)	
Occupation, n (%)			
Housewife	37 (62.7)	36 (57.1)	0.317 ^b
College student	3 (5.1)	5 (7.9)	
Private employee	13 (22.0)	10 (15.9)	
Civil servant	0 (0.0)	5 (7.9)	
Entrepreneur	2 (3.4)	2 (3.2)	
Not employed	4 (6.8)	5 (7.9)	
Duration of Illness from Diagnosis (years), (median (min- max))	4 (1-19)	6 (1-30)	0,009 ^{a*}

Note: Data analysis use ^a Independent T-test, ^b Fischer Exact

*significant if $p < 0,05$

Table 2. Fatigue measurement using Fatigue Severity Scale (FSS) based on LLDAS criteria

Variable	FSS ^a	Fatigue, n (%)	Not fatigue, n (%)	P value [*]
	Mean ± SD			
Non-LLDAS (n=32)	39.27 ± 10.3	39 (65.0)	21 (35.0)	<0.001 ^b
LLDAS (n=30)	30.25 ± 11.0	19 (30.2)	44 (69.8)	

Note: SD = Standard Deviation, n = frequency, ^aT test for FSS mean score in Non-LLDAS vs LLDAS group significant (p= <0.001); ^b Chi-square test

4. Discussion

This study revealed significant association between SLE disease activity based on LLDAS criteria and fatigue. Subjects from LLDAS group had lower incidence of fatigue than non-LLDAS group, nevertheless fatigue also an issue to patients in LLDAS group.

This finding aligned with study by Tench et.al. , in which patients with higher disease activity showed significant incidence of fatigue rather than those who had lower disease activity, but fatigue was still burdensome to patients with low SLE activity. In the study, *Systemic Lupus Activity Measure* (SLAM) and *European Consensus Lupus Activity Measure* (ECLAM) were utilized to measure disease activity, which fatigue was one determining components. ¹⁵

Fatigue is considered one of most important symptom and also contributes to physical, social and emotional malfunctioning. Study by Krupp et al. showed more than half SLE patients reported fatigue as most irritating symptom out of all SLE disease activity.¹⁶ Fatigue is an outcome from sickness behavior mechanism due to SLE disease activity. Proinflammatory cytokines, such as IL-1 β , IL-6, TNF- α play major role in pathophysiology of fatigue in SLE. In high SLE disease activity, more cytokines were produced; therefore there were higher incidence of fatigue. In the brain, those cytokines inducing a behavioral response called sickness behavior, characterized by fatigue, decreased physical activity, drowsiness, which were defense mechanism in avoiding any further damage. In high SLE disease activity, more cytokines were produced, therefore there were higher incidence of fatigue.¹⁷

Contradicted with study by Tench et al.¹⁵, Wang et al.¹⁸ suggested that there was no significant correlation between SLE disease activity and fatigue. In these studies, disease activity was measured by *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI) criteria, which did not include fatigue in the scoring. Study showed that fatigue was correlated with depression, which usually co-expressed in SLE patients.

Similarly, study by McKinley et al. reported there was no direct correlation between SLE disease activity and fatigue itself. This study use *Systemic Lupus Activity Measure minus Fatigue* (SLAM-F) criteria to evaluate SLE disease activity. SLAM-F criteria has no longer contains “fatigue” as scoring component as well as SLEDAI criteria. The study signified that SLE disease activity has no direct correlation with fatigue, but through another mediator variable such as sleep disruption and depression. ¹⁹

Unlike previous studies by Tench et al.¹⁵, Wang et al.¹⁸ and McKinley et al.¹⁹, subjects in this study were divided into two groups based on subject’s disease activity of LLDAS criteria. There are five criteria that must be fulfilled when using LLDAS criteria in evaluating SLE disease activity, in which SLEDAI-2K score ≤ 4 , SELENA-SLEDAI *physician global assessment* (PGA) ≤ 1 , no new lupus disease activity compared to the previous assessment, and also well tolerated and low dose medication. Patients spends more time in LLDAS have significantly reduced morbidity due to organ damage.¹²

This study revealed despite significant correlation between SLE disease activity based on LLDAS criteria and fatigue, fatigue consistently became an issue to subjects from LLDAS group. Fatigue can manifest from the disease

activity itself but also from other factors. Other factors which contributed to fatigue in SLE were mood disorders, disease control mechanisms, physical activities, depression, poor sleep quality, and psychosocial factors such as emotional distress, anxiety, quality of life and personality traits.^{20,21}

More than half subjects from both LLDAS and non-LLDAS group were housewives. Burgos et al.²² reported occupation affects subject's physical activity, thus physical activity was another factor that influence incidence of fatigue other than disease activity. Omdal et al.²⁰ reported among 57 subjects with low SLE disease activity based on SLEDAI criteria, there were no correlation between SLE disease activity and fatigue, however the strongest and most consistent factor was psychosocial factor. This corresponds well with other studies by Wang et al.¹⁸ and McKinley et al.¹⁹, which suggested no correlation between disease activity based on SLEDAI criteria and fatigue, nonetheless psychosocial factor was the one most contributing factor. There were high possibilities that fatigue was caused by other psychosocial factor that indicated high incidence of fatigue in LLDAS group. This study only measured fatigue using SLE disease activity based on LLDAS, but did not evaluated subject's psychosocial factors from both groups.

There are some limitations in this study. Duration of illness in LLDAS group was longer than non-LLDAS group, which could affect subject's disease coping mechanism, furthermore the incidence of fatigue. This study only measured fatigue using SLE disease activity based on LLDAS, but did not evaluated subject's psychosocial or other contributing factors from both groups. These subjects were not tested for depression with any depression diagnostic criteria such as Beck Depression Inventory or Patient Health Questionnaire 9 (PHQ 9). This was a preliminary study, hence determining how strong the correlation between SLE disease activity based on LLDAS and fatigue was not feasible.

5. Conclusion

This study showed significant association between LLDAS and fatigue. Lower fatigue level was found in LLDAS group in comparison to the non-LLDAS group.

Fatigue may be a distinct clinical manifestation of neuropsychiatric lupus and may be independent of lupus disease activity.

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