

Relationship Between Interleukin 6 (IL-6) and Organ Damage Based on SLICC Damage Index -SDI Score in Systemic Lupus Erythematosus Patients

Yesanopa Sianturi^{1*}, Deske Muhadi Rangkuti², Andi Raga Ginting²

¹Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, North Sumatera, Indonesia.

²Rheumatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, North Sumatera, Indonesia.

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*Corresponding author:

Yesanopa Sianturi

E-mail address:

elliorapasaribu@gmail.com

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A B S T R A C T

Background: Systemic Lupus Erythematosus (SLE) is a heterogeneous and complex chronic autoimmune disease. Interleukin 6 (IL-6) is a cytokine known to be elevated in people with SLE. This research was conducted to determine the relationship between IL-6 levels and organ damage based on the SLICC Damage Index-SDI Score in SLE patients.

Method: The study was a retrospective cross-sectional study involving 67 SLE patients conducted based on the SLICC 2012/ACR EULAR 2019 criteria at least 6 months prior to their inclusion. They were patients treated at the Rheumatology Clinic of Adam Malik General Hospital in Medan from June to August 2023, who met the inclusion and exclusion criteria. Organ damage assessment was done using the SLICC Damage Index (SDI) score, while disease activity degree was measured using the SLE Disease Activity Index (SLEDAI-2K) scoring system. **Results:** 94 % subject were women with a median SLEDAI-2K score of 6 (10 – 16) where the moderate degree of activity was the majority in this study (41.8%), followed by the mild degree (37.3%), severe (16, 4%), and remission (4.5%). The median IL-6 level was 63.3932 pg/ml (8.88 – 5966.67) where a significant correlation was found between IL-6 levels and the SDI score ($p=0.017$) and the degree of disease activity and the SDI score ($P<0.001$). **Conclusion:** A significant positive correlation was found between IL-6 levels and SDI scores in SLE patients ($p=0.017$).

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that can affect both men and women with the highest prevalence and incidence in young women, which is heterogeneous, complex and multisystem with significant morbidity and mortality.^{1,2} The etiology of SLE is still unclear, though autoantibody mechanism that causes tissue damage and systemic inflammation are thought to play key roles in pathogenesis.^{3,4} Diagnosis, treatment, and evaluation of complications remain challenging.^{5,6}

The lack of concrete biomarkers for assessing disease activity, selecting therapy, predicting flares, as well as evaluating treatment and

prognosis, poses a challenge in the management of SLE. Cytokines, including interleukin 6 (IL-6), are among the acute phase proteins that play a role in the development and activity of the immune system. IL-6 is a cytokine with both pro- and anti-inflammatory activity, which can increase in inflammatory conditions such as autoimmune diseases. This is supported by several studies on the relationship between IL-6 and SLE.^{8,9} It has been observed that an increase in IL-6 correlates with an increased risk of permanent or life-threatening organ damage. However, to date, no research has assessed the relationship between IL-6 levels and organ damage in SLE. Several studies have instead focused on assessing the relationship between IL-6 levels and disease activity and kidney damage.^{10,11}

For this reason, this research was conducted to determine the relationship between IL-6 levels and organ damage based on the SLICC Damage Index-SDI Score in SLE patients as an illustration of the prognosis of SLE.

2. Method

The study was a retrospective cross-sectional study after obtaining ethical clearance involving 67 SLE patients treated at the Rheumatology Clinic of Adam Malik General Hospital in Medan from June to August 2023. Inclusion criteria in this study are an age of at least 18 years, have diagnosed with SLE based on the SLICC 2012/ACR EULAR 2019 criteria at least 6 months prior, and willing to participate. The exclusion criteria are being pregnant or lactating, having an infectious condition (unless caused by disease progression or medication side effects), experiencing acute trauma or injury, and untreated SLE.

Serum IL-6 levels were examined using the ELISA method (Human FGF-23 ELISA Kit) with

blood sample taken from venous serum and processed using the Esco Swift TM Maxi Thermal Cycler, Esco Technologies Inc, in the Integrated Laboratory of the Faculty of Medicine, USU. Organ damage assessment was measured using the SLICC Damage Index (SLICC-DI) score assessment instrument with a score range of 0 – 47 and categorized based on organ damage domains, organ damage was measured based on a review of medical records for at least the last 6 months. The degree of disease activity was measured using SLEDAI 2K scoring which was assessed when the sample was included in the study.

The data obtained were analyzed using descriptive analysis, where the normality of the data was tested using the Kolmogorov Smirnov Test. The correlation test used the Spearman test, the relationship between the degree of disease activity and SDI used the Kruskal Wallis Test, while to assess the relationship between 2 independent groups used the Mann Whitney Test. SPSS 23 was used for the statistical analysis with a 95% confidence interval, where $p < 0.05$ indicates statistically significant.

3. Results

Table 1. Demographic, Clinical Characteristics and Domains of Organ Damage in Systemic Lupus Erythematosus

Characteristics	n = 67
Gender, n (%)	
Man	4 (6)
Woman	63 (94)
Age, years	
Mean±SD	35.3±9,775
BMI, n (%)	
Underweight	12 (17.9)
Normoweight	45 (65.7)
Overweight	8 (13.4)
Obesity	2 (3)
Comorbid	
DM Type 2	2 (2.98)
Hypertension	27 (40.29)
Dyslipidemia	3 (4.5)
Chronic Kidney Disease	2 (2.98)
Thyroid Disorders	2 (2.98)
Heart failure	1 (1.5)
SLEDAI-2K	

Median (min – max)	6 (0 – 16)
Degree of Disease Activity, n (%)	
Remission	3 (4.5)
Mild	25 (37.3)
Moderate	28 (41.8)
Severe	11 (16.4)
SDI	
Median (min – max)	1 (0 – 5)
Time of Diagnosis, months	
Median (min – max)	35 (6 – 183)
Treatment, n (%)	
HCQ	1 (1.5)
HCQ and steroids	4 (6)
Non-steroidal immunosuppressants and steroids	19 (28.4)
HCQ, non-steroids and steroids	34 (50.7)
HCQ and Non-steroids	8 (11.9)
Non-steroidal Immunosuppressants	1 (1.5)
Organ Damage and Comorbidities	
Kidney	26 (38.8)
Lungs	7 (10.4)
Musculoskeletal	5 (7.5)
Eye	11 (16.4)
Cardiovascular	6 (9)
Neuropsychiatric	11 (16.4)
Gonads	2 (3)
Skin	3 (4.5)
Blood vessel	3 (4.5)
Malignancy	2 (3)
DM Type 2	2 (3)

Abbreviation: BMI: Body Mass Index, DM: Diabetes Mellitus, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SDI: Systemic Lupus International Collaborating Clinics Damage Index, HCQ: Hydroxychloroquine

Table 2. Interleukin 6 levels in Systemic Lupus Erythematosus Patients

Interleukin 6, pg/mL	n = 67
Median (min – Max)	63.3932 (8.88 – 5966.67)

Table 3. Correlation of Interleukin 6 Levels with SDI Scores in Systemic Lupus Erythematosus Patients

	SDI Score	
	P	r
Interleukin 6	0.017¶	0.291*

¶Spearman Correlation

*p<0.05 is declared statistically significant

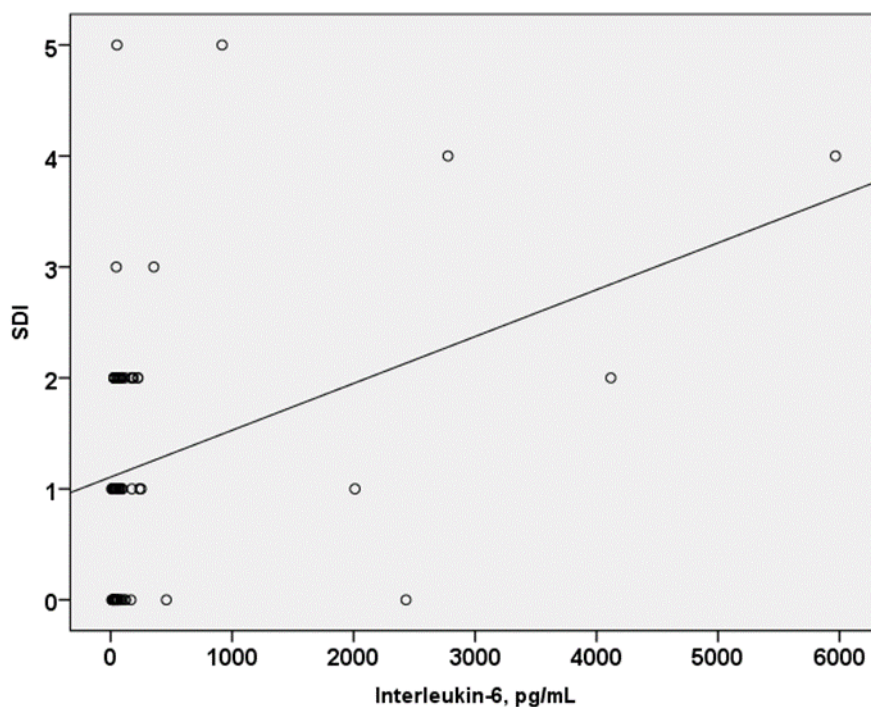


Figure 1. Scatterplot graph of the correlation between Interleukin 6 and SDI scores In Systemic Lupus Erythematosus Patients

Table 4. Correlation between the degree of disease activity and the SDI score in systemic lupus erythematosus patients

Degrees Disease Activity	n	SDI Score	p
		Median (Min-Max)	
Remission	3	-	0.001*
Mild	25	1 (0 – 2)	
Moderate	28	1 (0 – 5)	
Severe	11	2 (1 – 4)	

*Kruskal Wallis

Table 5. Relationship between Interleukin-6 Levels and Degree of Disease Activity in Systemic Lupus Erythematosus Patients

Degrees Disease Activity	n	Interleukin-6	p
		Median (Min-Max)	
Remission	3	87.32 (13.11-2431.12)	0.158*
Mild	25	46.05 (9.68-2010.84)	
Moderate	28	78.76 (8.88-5966.67)	
Severe	11	48.3 (25.31-2776.3)	

4. Discussion

In this study, the majority of research subjects were women (94%) with a mean age of $35.3 \pm 9,775$ year (Table 1). Bakshi et al. (2018) stated that SLE affects women 9 times more than men, with a prevalence between 20 and 40 years old¹² and Kono et al. (2021) stated that the frequency of obesity is higher in the SLE population compared to the normal population because the role of Vitamin D and Adipokines such as leptin and adiponectin in innate and adaptive immunity which makes individuals more susceptible to metabolic syndrome¹³, however this is contrary to our study where the majority of patients were normoweight (65.7%). Shamekhi et al.(2017) assessed body composition and basal metabolic rate in 74 women with SLE where the study showed a median (min-max) BMI of 26.3 (21.2–28.3) and no significant difference in BMI between patients with high or low SLEDAI.¹⁴

This study revealed that the most prevalent comorbidity among SLE patients was hypertension, observed in 27 individuals (40.29%). Mathis et al. (2013), in an experimental study conducted on mice, demonstrated a significant increase in blood pressure in SLE subjects compared to controls. This finding is closely linked to the involvement of renal innervation.¹⁵ Chamarti et al. (2011) investigating the relationship between IL-6, RAS activity, and hypertension, found that individuals with hypertension had higher baseline IL-6 levels compared to individuals with normotensive ($p < 0.001$). This is due to the Angiotensin II reaction to hypertension that is dependent on the mineralocorticoid receptor.¹⁶ Other comorbid also have correlation with IL-6 levels in different ways. A study by Mikkawy et al.(2020) found that IL-6 levels increased considerably in overweight and obese persons. This is based on overweight and obese individuals' "macronutrient excess" in adipose tissue increases inflammatory adipokines such as IL-6/17. CKD patients often have elevated

plasma IL-6 levels, which can be attributed to oxidative stress, chronic inflammation, or fluid overload. Meanwhile, decreased renal function reduces IL-6 clearance, contributing to its buildup. In patients with end-stage renal disease (ESRD), therapeutic hemodialysis and peritoneal dialysis induce inflammatory responses and increase IL-6 production.¹⁸ According to a study conducted by Naser and Thikra (2024), there is a significant difference in the mean concentration of IL-6 among patients with thyroid groups, when compared to the concentration mean of the control group. IL-6 play an important role in controlling the development, differentiation, and activation of cells during inflammatory and immunological responses. Individuals with hyperthyroidism and hypothyroidism had significantly lower IL-6 levels.¹⁹ Chia, Chin, et al. (2021) found that individuals with heart failure had greater systolic and diastolic blood pressure, as well as higher levels of IL-6.²⁰ However, Zucchi et al. (2023), in a review, indicated that the complexity of SLE encompasses not only multi-organ involvement but also the presence of comorbidities that may manifest before or during the course of SLE itself.²¹ Therefore, it can be inferred that comorbidities may act as exacerbating factors or complications of SLE.

In this study, the median SLEDAI score (Table 1) was 6 (range 10-16), with the majority of patients exhibiting a moderate degree of activity (41.8%), followed by mild (37.3%), severe (16.4%), and remission (4.5%). Thus, it can be concluded that the majority of research subjects were in an active condition. The median (range) duration of diagnosed SLE was 35 (6-183) months, and the median (range) SDI score in this study was 1 (0-5). The most commonly affected organ domain was the kidney, accounting for 38.8% of cases, followed by the eyes and neuropsychiatric (NPSLE) domains, each at 16.4%. This finding aligns with research by Yap et al. (2015), which indicates that kidney manifestations are the most frequent and severe organ involvement in lupus, particularly among Asians.²² Retinal toxicity is a known side effect of HCQ usage, often correlated with the duration of drug intake. Typically,

such toxicity is rare within the first 5 years of HCQ use at doses below 6.5 mg/kg/day, with only a 1% incidence within the initial 10 years.²³ In this study, HCQ doses were consistently below 6.5 mg/kg/day, but an analysis of HCQ usage duration and retinal toxicity was not conducted. Cataracts are another form of organ damage whose incidence rises, particularly after 5 years of disease progression. This increase may be exacerbated by comorbidities or as a consequence of long-term steroid use.²⁴ Neuropsychiatric disorders typically manifest within 5-15 years of lupus onset.

The predominant treatment regimen observed in this study was a combination therapy involving HCQ, non-steroidal immunosuppressants, and steroids, comprising 34 samples (50.7%). Notably, the treatment type recorded in this study reflects the final treatment administered to patients during their involvement in the study, without considering their prior treatment history. This finding aligns with previous research indicating the influence of disease activity, duration of diagnosis, comorbidities, and treatment modalities, especially steroids, on organ damage.²⁵ However, in this study, organ damage assessment relied solely on existing medical records. This limitation is tied to the Health Insurance System, where supplementary examinations to detect organ damage are typically indicated only in response to patient complaints or symptoms.

In this study, the median (range) level of IL-6 (Table 2) was 63.3932 pg/ml (8.88 - 5966.67). Grebenciucova et al. (2023) described IL-6 as a pleiotropic cytokine, acting as an acute phase reactant that influences various immune processes such as B and T lymphocytes, brain barrier permeability, synovial inflammation, and hematopoiesis. It is produced by B and T lymphocytes, macrophages, and dendritic cells in response to inflammatory conditions, infections, or stress. Normal levels of IL-6 in healthy individuals are typically below 7

pg/ml.²⁶ Jacob et al. (2011) reported that serum IL-6 levels correlate with SLE disease activity and response to therapy. IL-6 also shows specific associations with clinical manifestations, such as elevated levels found in the cerebrospinal fluid of SLE patients with psychosis and in the urine of those with lupus nephritis.²⁷ In this study, level of IL-6 was higher in remission group, there were 3 subjects in the remission group, which is certainly less proportional to the mild/moderate/ severe group. These three subjects had IL-6 levels: 13.11 pg, 87.3183 pg, 2431.12 pg where the first subject was diagnosed for 56 months and the next 2 subjects with a diagnosis duration of 18 months, it is necessary to further examine whether the duration affects IL-6 levels, other conditions that trigger an increase in IL-6 such as body mass index, lifestyle or due to the influence of the selection of disease activity classification in this study using SLEDAI-2K because something similar can also be seen in the study by Salvans et al. (2023) which showed no significant correlation between IL-6 and disease activity with SLEDAI-2K.²⁸

This study found a significant correlation but weak between IL-6 levels and SDI scores ($p=0.017$) with a correlation coefficient of 0.291 (Table 3), suggesting a potential role for IL-6 in predicting organ damage in SLE patients. This finding suggests that higher IL-6 levels are associated with higher SDI scores (Figure 1). It has been proposed that IL-6 stimulates autoantibody synthesis by boosting autoreactive B lymphocyte proliferation and the differentiation of naive B cells into plasma cells. In addition, IL-6 may increase the expression of recombination-activating genes which leads to autoantibody overproduction in SLE. IL-6 activates the STAT3 pathway, promoting the differentiation of naïve CD4+ T cells into Th17 cells. However, it also impairs Treg differentiation, suggesting that IL-6 may contribute to SLE development by mediating the Th17/Treg imbalance. Notably, a prior study found that IL-6 could improve vascular permeability by stimulating the release of vascular endothelial growth factor from fibroblast-like synoviocytes, hence boosting inflammatory cell infiltration and immune

complex deposition. Thus, IL-6 may contribute to SLE development by decreasing vascular endothelial function. Taken together, this evidence supports our conclusion that high blood IL-6 levels are associated with tissue damage.²⁷ Consequently, this biomarker could be considered a predictor of organ damage, disease prognosis, and the potential effectiveness of anti-IL-6 therapy in managing SLE.

This study reveals a significant relationship between the degree of disease activity and the SDI score ($P < 0.001$), indicating that higher disease activity correlates with higher SDI scores. The group with the heaviest disease activity exhibited the highest median SDI score (Table 4). Longitudinal studies have shown that disease activity plays a crucial role in organ damage, which is influenced by factors such as comorbidities and therapy.²⁴ However, when examining the connection between IL-6 levels and the degree of disease activity (Table 5), no significant relationship was found between IL-6 levels and the degree of SLE disease activity ($p = 0.158$). Interestingly, the group with the highest median IL-6 levels was the one with the current degree of activity. Ding et al. (2020), in a meta-analysis, reported that IL-6 levels were elevated in the SLE population compared to the normal population and showed a positive correlation with disease activity. However, when SLEDAI-2K exceeded 4 (defined as active disease), there was no correlation between IL-6 levels and disease activity. This suggests that the definition of disease activity might introduce heterogeneity in the correlation between IL-6 levels and SLE activity.²⁷ This variability could stem from the subjectivity involved in measuring the SLEDAI-2K score and the incomplete fulfillment of laboratory criteria required for calculating the SLEDAI-2K, as not all subjects underwent the necessary laboratory examinations during the study. This study has several flaws, including the fact that it does not describe the process of disease development,

including influencing factors such as whether comorbidities arise before or after lupus is diagnosed, relapse conditions, compliance with treatment, and others, so it is impossible to conclude whether exposure precedes the disease or vice versa, and risk factors cannot be measured accurately, affecting the study's results. Organ damage assessment was reliance on medical records.

5. Conclusion

This study shows significant positive relationship between IL-6 levels and SDI scores in Systemic Lupus Erythematosus patients ($p = 0.017$), suggesting IL-6 could be a useful biomarker for predicting organ damage

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