Exploring the Link Between Interferon-gamma Levels and Lupus Severity Using SLEDAI-2K and SLICC Damage Index

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***Abstract*- Introduction:** SLE is a chronic autoimmune disease that causes organ damage and has diverse clinical symptoms. High morbidity and mortality are linked to increased disease activity. The interferon signaling pathway is activated in SLE cases, but its link to higher SLE disease activity remains unclear. This study aims to investigate the role of IFN-gamma in influencing the activity level of organ damage in SLE.

Methods: Following inclusion and exclusion criteria, this cross-sectional study was conducted over 6 months at H. Adam Malik Hospital Medan. The data collected included clinical manifestations, SLEDAI and SLICC Damage Index (SDI), and IFN-gamma levels. The impact of IFN-gamma on the extent of organ damage activity was assessed using a correlation test. Linearity and correlation strength were considered statistically significant, as indicated by a p-value less than 0.05.

Result: The study included 67 patients, mostly women (9:1 ratio), with an average age of 35. Moderate disease activity was observed at 41.8%, the median SDI organ damage score was 1, and the median IFN-gamma level was 31.16 pg/mL. The mean interferon-gamma levels exhibited a progressive increase corresponding to the severity of disease activity. Specifically, the levels were 39.48 ±28.65 during remission, 93.49±105.5 with mild disease activity, 200.55±374 in moderate cases, and 208.84±336 in severe cases. IFN-gamma showed no significant correlation with disease activity (SLEDAI) or the SLICC Damage Index (SDI), with r values of +0.055 (p = 0.659) and +0.083 (p = 0.506).

Conclusion: Interferon-gamma levels do not correlate with disease severity or organ damage in SLE patients.

Keywords: SLE, IFN-Gamma, SLEDAI, SLICC Damage Index

I. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by inflammation of connective tissue1. SLE can affect all organs, and its clinical presentation varies significantly among individuals 2. The reported incidence and prevalence of SLE in the Asia-Pacific region ranges from 0.9 to 3.1 per 100,000 people annually and 4.3 to 45.3 per 100,000 people 3-4. In Indonesia, several hospitals have documented an increasing trend in SLE cases, rising from 17.9-27.2% in 2015 to 30.3-58% in 2017 5. This increase in incidence is associated with the progression of SLE disease activity.

The primary goal in managing Systemic Lupus Erythematosus (SLE) is to achieve low disease activity through effective treatment 6,7. As outlined by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), the main objectives include attaining complete remission, maintaining low disease activity, and achieving partial or complete renal remission. Approximately 20-30% of individuals with SLE experience a persistently active disease. Addressing the prevention of chronic damage, especially in the early stages of the disease, remains an unmet need in SLE patient management. Hence, all SLE patients must undergo regular follow-up assessments to monitor disease activity. The SLE Disease Activity Index (SLEDAI) is the most widely used tool for measuring SLE disease activity 8. Furthermore, it is essential to assess the degree of chronic organ damage that has accrued since the disease diagnosis utilizing the SLICC damage index.

Genetic factors are linked to a higher risk and severity of SLE. The histocompatibility region of leukocyte antigen (HLA) increases the risk of systemic lupus erythematosus (SLE) and other autoimmune disorders 2,3. Additionally, mutations

in the interferon regulatory factor 5 (IRF5) gene have also been linked to a heightened risk of developing SLE. Over 50% of patients exhibiting various IFN-inducible genes (IFIGs) demonstrate an association with increased severity and activity of the disease 9. IFN-gamma (IFN-γ) levels are linked to arthritis, nephritis, and anti-Ro60 antibodies. Excess IFN-γ can cause chronic inflammation, leading to organ damage in SLE patients. Studies have identified that activated IFN-γ pathways are associated with increased disease activity in patients with SLE 10-15. Additionally, polymorphisms in the IFN-γ gene have been linked to a higher susceptibility to developing SLE. However, a direct correlation between elevated IFN-γ levels and the severity of disease activity or organ damage in SLE patients has not been established

II. METHODS

The study involves a systemic lupus erythematosus patient at H. Adam Malik Hospital Medan, who consented to participate from November 2023 to May 2024. This study employs a cross-sectional design, considering a minimum sample size of 36 participants who meet the following inclusion and exclusion criteria: individuals over the age of 18, diagnosed with SLE according to the EULAR/ACR 2018 diagnostic criteria for a duration of at least 6 months, currently receiving an appropriate therapy regimen, willing to undergo interferon gamma testing, and capable of cooperating in assessing disease progression using the SLEDAI score and SLICC damage index. SLE patients with secondary infections, cancer, estrogen therapy, and other autoimmune diseases were excluded from this study.

Patient data, complaints, and clinical manifestations were assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the SLICC Damage Index (SDI). SLE severity is categorized as mild (SLEDAI <6), moderate (SLEDAI 6-12), and severe (SLEDAI ≥12). The SDI tracks permanent damage in 12 organ systems: eye (0-2), neuropsychiatry (0-6), kidney (0-3), lung (0-5), cardiovascular (0-6), peripheral blood vessels (0-5), gastrointestinal tract (0-6), musculoskeletal (0-7), skin (0-3), endocrine (diabetes) (0-1), gonads (0-1), and malignancy (0-2). Damage can only remain stable or increase, with a theoretical maximum of 47 points. Interferon-gamma levels were measured using human IFN gamma ELISA kits with 1 mL blood samples from the research subjects.

Categorical data is shown as frequency and percentage distributions. Numerical data follows normality test results: parametric data as means and standard deviations and non-parametric data as medians (min-max values). For parametric data correlation, use Pearson's test; for non-parametric, use Spearman's test with SPSS version 20. Correlation linearity (r) and direction (positive/negative) are noted, with statistical significance at $p<0.05$

III. RESULTS

The study included 67 patients, mostly women (9:1 ratio), with an average age of 35. Table 1 shows the demographic characteristics of the subjects. Most were female (63 people, 94%). The average age was 35.3 years, ranging from 18 to 59 years. The median SDI score for organ damage was 1.00 (0.00-5.00). The median diagnosis time was 35 months (6-183 months). The median IFN-Gamma value was 31.16 (range: 0.92-1874.85).

Table 1. Baseline characteristics of subjects

Parameters	**n (%)**
Gender	
Male	4 (6,0)
Female	63 (94,0)
Age, year	
Mean (SD)	35,3 (9,78)
Degree of disease activity (SLEDAI)	
Median (Min-Max)	6 (0 – 16)
Remission	3 (4,5)
Mild	25 (37,3)
Moderate	28 (41,8)

Severe	11 (16,4)
Degree of damaged organ (SDI)	
Median (Min-Max)	1 (0 – 5)
Long Diagnosed, month	
Mean (SD)	47,06 (41,23)
IFN-Gamma	
Median (Min – Max)	31,16 (0,92 – 1874,85)
Treatment	
HCQ	1 (1,5)
HCQ and steroid	4 (6)
Imunosupresan and steroid	19 (28,4)
HCQ, imunosupresan and steroid	34 (50,7)
HCQ and imunosupresan	8 (11,9)
Imunosupresant	1 (1,5)
Total	67 (100,0)

Note: n(%): sample size in percentage.

Organ damage and comorbidities in the study subjects with SLE are shown in Table 2. The kidneys were affected in 26 individuals (38.8%), followed by the eyes and neuropsychiatric systems in 11 individuals (16.4%), and the lungs in 7 individuals (10.4%). Violence and diabetes mellitus were present in 2 individuals each (3%).

Table 2. Domain Analysis of Organ Damage and Comorbidities in SLE Patients

Organ damage and comorbidities	**n (%)**
Kidney	
Yes	26 (38,8)
None	41 (61,2)
Lung	
Yes	7 (10,4)
None	60 (89,6)
Musculoskeletal	
Yes	5 (7,5)
None	62 (92,5)
Eye	
Yes	11 (16,4)
None	56 (83,6)
Cardiovascular	
Yes	6 (9,0)
None	61 (91,0)
Neuropsychiatry	
Yes	11 (16,4)
None	56 (83,6)
Gonad	

Yes	2 (3,0)
None	65 (97,0)
Skin	
Yes	3 (4,5)
None	64 (95,5)
Vascular	
Yes	3 (4,5)
None	64 (95,5)
Malignancy	
Yes	2 (3,0)
None	65 (97,0)
Diabetes mellitus	
Yes	2 (3,0)
None	65 (97,0)

Table 3 presents the mean Interferon-gamma levels by disease activity degree. In remission, the level averaged 39.48 (SD 28.65). For mild cases, it was 93.49 (SD 105.50). Moderate cases averaged 200.55 (SD 374.98), and severe cases averaged 208.84 (SD 336.99).

Table 3. Average IFN-gamma levels based on the degree of SLE disease activity

Degree of Disease Activity	**Interferon-gamma levels Mean (SD)**
Remission	39.48 (28.65)
Mild	93.49 (105.50)
Moderate	200.55 (374.98)
Severe	208.84(336.99)

Note: SD = standard of deviation

Table 4 shows the correlation between IFN-Gamma and Systemic Lupus Erythematosus (SLE) activity. The Spearman correlation test found no significant relationship (*p-value* > 0.05) between IFN-Gamma, organ damage, and SLE activity level in the 67 participants. The positive correlation was very weak (r < 0.199).

Table 4. IFN-gamma correlation to SLEDAI and SDI

	Degree of Disease Activity (SLEDAI)	**Degree of SLICC Damage Index (SDI)**
IFN Gamma	r =+0,055	r =+0,083
	p= 0,659	p= 0,506
	n=67	n=67

Note: *significant at p<0.05, SD = standard of deviation; r=coefficient correlation, n=sample size.

IV. DISCUSSION

In this study, 63 out of 67 subjects (94%) were female, with an average age of 35. This finding is consistent with previous research, which indicated that patients with systemic lupus erythematosus (SLE) are predominantly women, averaging 34 years of age [16]. The median interferon-gamma level observed in this study was 31.16 pg/ml. Specifically, the levels were categorized as follows: 39.48 pg/ml for remission, 93.49 pg/ml for light activity, 200.55 pg/ml for moderate activity, and 208.84 pg/ml for severe activity.

SLE patients had an average disease duration of 47.06 months in this study. Saeed Mohammadi et al. (2017) identified a positive correlation between SLE disease activity, as measured by SLEDAI, and interferon-gamma levels, with higher levels observed in new-onset patients.? Research has examined the role of IFN-γ in SLE, indicating that higher levels of these cytokines may be linked with greater disease activity. Increased levels of IFN-γ have been documented in patients with active Systemic Lupus Erythematosus (SLE) compared to those in remission, indicating its potential utility as a biomarker for disease activity. IFN-γ can contribute to SLE pathogenesis by promoting Th1 cell differentiation, which increases pro-inflammatory cytokines and autoantibodies. This amplifies inflammation, leading to tissue damage typical of SLE [16-18].

Furthermore, IFN-γ has been implicated in macrophage activation and antigen presentation promotion, which are important in maintaining an autoimmune response in SLE. The constant activation of these immune cells can lead to chronic inflammation and worsen the disease process. Interestingly, IFN-γ also affects the function of B cells, which are responsible for producing autoantibodies in SLE. By increasing the activation and differentiation of B cells, IFN-γ further contributes to the production of pathogenic autoantibodies that attack the body's own tissues [16].

This study found no significant relationship between interferon-gamma levels and the degree of SLE disease activity ($p = 0.659$). The relationship between IFN-γ and SLE is not entirely clear. Some studies did not report significant correlations, suggesting that other factors, such as genetic polymorphism, steroid therapy and immunosuppressants, and disease duration, may modulate the impact of IFN-γ on disease activity [16,17, 19]. Saeed Mohammadi et al. stated that there are higher levels of interferon-gamma in the new onset of SLE patients. Manman Liu et al noted that the level of Interferon type I activity affects the level of Interferon-gamma and disease activity. Compared to patients with low type I IFN scores, patients with high type I IFN scores showed improved type II IFN and SLEDAI scores.

Using corticosteroids and/or immunosuppressants also affects interferon-gamma levels in SLE patients. In this study, the treatment was predominantly combined with HCQ, immunosuppressants, and corticosteroids in 34 patients (50.7%). Victor Moreno et al stated that corticosteroids and combining corticosteroids and immunosuppressants had a negative and significant correlation with interferon-gamma levels. Manman Liu et al corticosteroid therapy dose also affects interferon-gamma levels. In the study, the subjects were divided into two groups based on the dose of prednisone: the low-dose group (≤ 10 mg/day) and the medium to high-dose group (>10 mg/day). Both groups tended to have lower IFNG expression levels than starting-out patients. The moderate to high dose group showed lower IFN-II scores than new-onset patients [19].

The Signal Transducer Activator of Transcription 4 (STAT4) is crucial in SLE disease activity. STAT4 activates gene transcription for TH1 and Th17 lymphocytes, mainly producing IFN gamma and IL-17A. Guerrero et al. (2023) found that the TT genotype of the STAT4 gene rs7574865 boosts gamma IFN levels more than GG or GT genotypes, indicating a higher risk for increased IFN [19]. SDI assesses cumulative organ damage in SLE patients, focusing on irreversible damage present for at least six months, regardless of cause. Damage may result from the disease, complications, or treatment side effects. The index includes 41 items across 12 organ systems: eye, neuropsychiatry, kidney, pulmonary, cardiovascular, peripheral blood vessels, gastrointestinal, musculoskeletal, skin, endocrine systems, malignancies, and other types of damage [20-21].

This study found no significant relationship between Interferon-gamma levels and organ damage assessed by SDI ($p = 0.506$). Kidney damage was most common (38.8%), followed by eye (16.4%) and neuropsychiatric (10.4%) damage. Few studies have explored the correlation between Interferon-gamma levels and organ damage. However, Oke et al. (2019) indicated that high IFN-γ and type I IFN activity were linked to severe SLE with nephritis and arthritis, while increased IFN-α was associated with active mucocutaneous inflammation and milder cardiovascular symptoms[22].

A study conducted by Victor Moreno et al. (2022) found that interferon gamma is significantly associated with anti-dsDNA positivity ($p = 0.007$)[19]. The unrelated results in this study could be ascribed to the duration of SLE disease, which has an average length of 46 months. This finding aligns with research by Ghazali et al. (2018) in Malaysia, indicating that the SDI score significantly correlates with longer disease duration, with an average length of 6.57 years [21]. IFN-γ is considered a potential target for therapeutic interventions in SLE. Targeting IFN-γ or its downstream signaling pathway may help reduce inflammation and prevent organ damage in SLE patients. Clinical trials are currently investigating the efficacy of IFN-γ inhibitors in decreasing disease activity and preventing organ damage in SLE [5].

This study has several limitations. It does not consider factors that might influence interferon-gamma levels, such as treatment duration, onset of diagnosed SLE, nutritional status, and family history of autoimmunity. Further studies should examine factors influencing interferon-gamma levels and disease activity, such as gene polymorphisms encoding interferon-

gamma, treatment regimen effects, or interferon type I activity. Unlike the current study, future research should ensure an even sample distribution across groups, in which the HCQ and immunosuppressant groups each have only one sample

V. CONCLUSION

Interferon-gamma levels do not correlate with disease severity SLEDAI or organ damage SLICC Damage Index in SLE patients

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