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Correlation of TNF-α with Systemic Lupus Erythematosus Activity in Mohammad Hoesin Hospital Palembang

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Abstract

Systemic lupus erythematosus (SLE) is a persistent autoimmune disorder marked by immunological dysregulation and widespread inflammation. Tumor necrosis factor-α (TNF-α), a pivotal pro-inflammatory cytokine, has been associated with the pathophysiology of systemic lupus erythematosus (SLE), although its clinical relevance is still debated. This study aims to assess the connection between serum TNF-α levels and disease activity, as quantified by the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI), in Indonesian patients with systemic lupus erythematosus (SLE). A cross-sectional study was performed including 34 patients exhibiting mild-to-moderate systemic lupus erythematosus activity (MEX-SLEDAI ≤12) at Dr. Mohammad Hoesin General Hospital in Palembang, Indonesia. Individuals with significant active disease were excluded. Serum TNF-α concentrations were quantified via a commercial ELISA kit, while disease activity was evaluated through MEX-SLEDAI. Correlation analysis was conducted using Spearman's rank test, with $p < 0.05$ being statistically significant. The average age of participants was 33.6 ± 11.0 years, with 94.1% identifying as female. The median MEX-SLEDAI score was 3 (range 2–7), and the median TNF-α level was 1.834 pg/mL (range 0.99–8.62). No substantial connection was detected between serum TNF-α levels and disease activity ($r = 0.111$, $p = 0.533$). This suggests that serum TNF-α levels did not correlate with or forecast clinical disease activity in this investigation. The results indicate that the efficacy of TNF-α as a biomarker in SLE may be contingent upon contextual factors, especially illness severity. Additional multicenter and longitudinal studies involving individuals with a broader spectrum of disease activity are necessary to elucidate its clinical significance.

Keywords : Systemic Lupus Erythematosus, TNF-α, MEX-SLEDAI, Cytokines

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune condition characterized by a loss of self-tolerance, the production of autoantibodies, and the buildup of immune complexes, leading to significant inflammation and tissue damage. The clinical presentation of systemic lupus erythematosus (SLE) is markedly variable, encompassing modest mucocutaneous symptoms to severe organ involvement, including lupus nephritis and neuropsychiatric lupus.[1]

The pathogenesis involves a complex interplay of genetic, environmental, and hormonal factors, culminating in immune dysregulation. Central to this process are cytokines, which orchestrate the inflammatory cascade.[2] Tumor Necrosis Factor-α (TNF−α) is a potent pro-inflammatory cytokine known to be elevated in many autoimmune conditions. TNF−α modulates maintenance and maintenance of inflammatory processes, inducing apoptosis and cell death.[3] In SLE, its role is complex; while it can promote inflammation and

tissue injury, it also appears to have regulatory or even protective functions, a phenomenon often described as the "TNF−α paradox".[4–6]

Previous studies investigating the relationship between serum TNF−α levels and SLE disease activity have yielded conflicting results. Some have reported a positive correlation, particularly in patients with active nephritis, while others have found no significant association. SLE.[7–11] This disparity may be due to variations in patient groups, especially regarding illness severity, and the particular disease activity indicators employed. This study aimed to ascertain the relationship between serum TNF−α levels and disease activity, evaluated through the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI), in a designated cohort of Indonesian patients at Dr. Mohammad Hoesin Hospital, Palembang, due to the prevailing uncertainty and the necessity for dependable biomarkers.

2. Methods

This study was a cross-sectional analysis of baseline data collected from a larger parent study, "Adjunctive Use of Vitamin C Reduces Inflammatory Markers and Clinical Activity in SLE: A Randomized Controlled Study". The study was conducted at the Allergy Immunology Clinic of Dr. Mohammad Hoesin Hospital in Palembang, Indonesia.

Patients included in this study are patients with mild-moderate SLE activity (defined as a MEX-SLEDAI score ≤12). Patients with severe, active disease (e.g., active nephritis, severe neurological involvement) or those on high-dose immunosuppressants were excluded due to ethical considerations and potential for harm in the context of the main trial. This study has obtained permission from the Ethics Committee of RS Mohammad Hoesin, Ministry of Health of the Republic of Indonesia (No.DP.04.03/D.XVIII.06.08/ETIK/ 204/2024).

The study was conducted at the Inpatient Ward and Outpatient Clinic of Allergy and Clinical Immunology, Department of Internal Medicine, Mohammad Hoesin General Hospital, Palembang, Indonesia. Patient recruitment and sample collection were carried out between November 2024 and March 2025. Disease activity was prospectively assessed by a trained internist using the MEX-SLEDAI. The MEX-SLEDAI is a validated tool that scores 24 clinical and laboratory parameters present in the preceding 10 days. Venous blood samples were collected from each participant at baseline. Serum was separated, aliquoted, and stored until analysis. Serum TNF−α levels were quantified utilizing a commercial quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit, in accordance with the manufacturer's guidelines. The outcomes were quantified in picograms per milliliter (pg/mL).

Data were evaluated utilizing SPSS version 25.0. Descriptive statistics were employed to encapsulate patient features. The Shapiro-Wilk test was employed to evaluate data distribution. If the data for TNF−α and MEX-SLEDAI were not regularly distributed, the link between the two variables was assessed using Spearman's rank correlation coefficient; otherwise, the Pearson test was employed. A two-tailed p-value below 0.05 was deemed indicative of statistical significance.

3. Results

A total of 38 patients with mild-moderate SLE activity (defined as a MEX-SLEDAI score ≤12). Four participants were excluded due to dropout (2 severe flares, 1 hospitalization, 1 lost to follow-up), resulting in a final sample of 34 patients. In this study 32 (94.1%) were female. The median age of the participants was 34 (17-57) , and the disease duration was mostly <5 years (73.5%, 25 patient). Majority of participants in this study were non obese (22 patient, 64.7%). The median serum TNF−α level for the cohort was 1.83 pg/mL. The median MEX-SLEDAI score was 3, confirming that the patient population predominantly had mild-to-moderate disease activity.

Table 1. Demographic and Clinical Characteristics

Variable	N	%
Sex		
Male	2	5.9
Female	32	94.1
Duration since SLE diagnosis		
<5 years	25	73.5
≥5 years	9	26.5
Comorbidity : Diabetes Mellitus		
DM	0	0.0
No DM	34	100.0
Comorbidity: Hypertension		
Hypertension	10	29.4
No hypertension	24	70.6
BMI		
Non-obese (≤25)	22	64.7
Obese (>25)	12	35.3

Table 2. Age, Laboratory Findings, and Disease Activity of Study Participants

Variable	Mean ± SD	Median (min–max)
Age (years)	33.56 ± 11.03	33.50 (17-57)
TNF-α *baseline (pg/mL)*	2.19 ± 1.38	1.83 (0.99-8.62)
MEX-SLEDAI *baseline*	3.12 ± 1.20	3 (2-7)

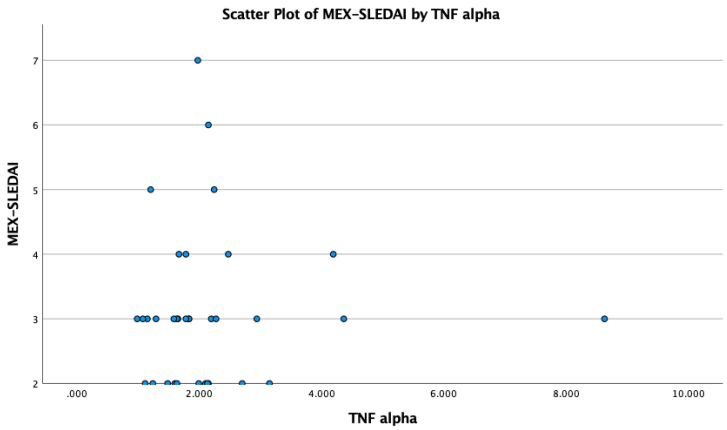

Figure 1. Scatter plot of TNF- α levels and MEX-SLEDAI scores

Bivariate Analysis

The primary analysis aimed to assess the correlation between serum TNF−α levels and MEX-SLEDAI scores. The scatter plot of the data did not show a clear linear relationship between the two variables (Figure 2).

The Spearman's correlation analysis confirmed this observation. There was no statistically significant correlation found between serum TNF−α levels and MEX-SLEDAI scores ($r = 0.111$, $p = 0.533$). This indicates that in this patient group, higher levels of serum TNF−α were not associated with higher clinical disease activity as measured by MEX-SLEDAI.

4. Discussion

In this study, the majority of participants were female. Systemic lupus erythematosus (SLE) affects women predominantly during their reproductive years due to the immune-modulating effects of estrogen. Estrogen, particularly estradiol, interacts with estrogen receptors (ERs) on immune cells, altering gene expression and influencing autoantibody production and immune cell function.[12]

Most patients also had a disease duration of less than five years, indicating that severe clinical manifestations and major organ involvement were not yet predominant. Furthermore, the majority of patients had no major comorbidities such as diabetes mellitus or hypertension, and most were classified as non-obese. The absence of cardiometabolic risk factors reduces the likelihood of additional systemic inflammation that could elevate TNF-α levels. Adipose tissue, especially visceral fat, acts as an active endocrine organ that secretes adipokines and pro-inflammatory cytokines, such as TNF-α, resulting in a condition of low-grade chronic inflammation. In diabetes, chronic hyperglycemia triggers oxidative stress and the formation of advanced glycation end products (AGEs), which activate the NF-κB pathway and enhance TNF-α production, whereas hypertension contributes through endothelial dysfunction and the release of vascular inflammatory mediators. The combination of these mechanisms results in higher TNF-α levels in SLE patients with cardiometabolic comorbidities compared to those without, thereby exacerbating inflammation and increasing the risk of cardiovascular complications.[13–15]

TNF-α is considered a "master regulator" of pro-inflammatory cytokine production. In addition to pro-inflammatory cytokines, TNF-α also amplifies lipid signal transduction mediators, including prostaglandins and platelet-activating factor.[16] The attachment of microbes or endogenous ligands to toll-like receptors triggers either the MyD88 or TRIF pathways. Depending on the molecule, attachment to TLR1, TLR2, TLR7, or TLR9 transmits signals through the MyD88 pathway, while TLR3 transmits signals through the TRIF pathway. Once stimulated, both of these pathways activate NF-kB in the cell nucleus, which then initiates the transcription of TNF-α. Other proteins such as ERK, JNK, and p38 are also activated, leading to the production of this cytokine. Physiologically, this cytokine can help kill bacteria and repair tissue. However, if cytokine dysregulation occurs, the chronic inflammatory process can be prolonged, and tissue damage may result. TNF-α is posited as a pivotal factor in the activation and recruitment of inflammatory cells and is thought to significantly contribute to the

pathogenesis of numerous chronic inflammatory disorders.[5]

The role of TNF-α in the pathogenesis of SLE remains contentious; some studies assert that TNF-α contributes to susceptibility to SLE, whereas others characterize its role as protective in SLE patients, a phenomenon referred to as the TNF-α paradox. Numerous studies indicate that TNF-α, in conjunction with other cytokines like IFN-α, IL-12, IL-4, IL-10, and IL-6, are pivotal cytokines in systemic lupus erythematosus (SLE). Svenungsson et al. highlighted elevated triglyceride and diminished high-density lipoprotein (HDL) levels as indicators of disease activity, alongside higher TNF-α/TNFR levels in patients with systemic lupus erythematosus (SLE), and the association between inflammation, dyslipoproteinemia, and cardiovascular disease. Moreover, elevated levels of TNF-α have been seen in the bloodstream and renal inflammation of patients with systemic lupus erythematosus (SLE). Elevated TNF-α levels were correlated with illness severity in patients with SLE. Elevated serum concentrations of TNF-α and its soluble receptors have been noted in SLE patients with active disease in contrast to those with inactive disease. Moreover, SLE patients exhibiting elevated TNF-α levels possess T lymphocytes that are more prone to apoptosis compared to T cells from healthy individuals. The heightened TNF-α-induced apoptosis elevates the autoantigen burden, hence intensifying the autoimmune response in patients with SLE. In contrast, certain researchers have noted reduced TNF-α levels in SLE patients, especially those with severe disease. Reduced levels of the TNF-α adaptor protein are correlated with heightened lymphocyte apoptosis and substantial autoantibody production, leading to immunopathogenic damage in patients with systemic lupus erythematosus (SLE).[4] Several research have indicated no correlation between polymorphisms in the TNFR2 gene and systemic lupus erythematosus (SLE). Sullivan et al. investigated the genetic frequency of SNPs in the 3' untranslated region of TNFR2 in individuals with systemic lupus erythematosus and found no connection, but the study exclusively focused on Caucasian patients.[5]

This study found no significant correlation between serum TNF−α concentrations and SLE disease activity in patients with mild-to-moderate disease. These findings are in line with McCarthy et al. who also reported no significant correlation between TNF-α levels and overall disease activity in mild SLE. In contrast, Svenungsson et al. found elevated TNF-α/TNFR in patients with higher disease activity, particularly in those with nephritis. This discrepancy highlights that TNF-α may only emerge as a robust biomarker in patients with more severe manifestations.[7,9] It is also possible that the widespread use of hydroxychloroquine contributed to the lack of association, as hydroxychloroquine is known to modulate cytokine production, including TNF-α.[17]

The most plausible explanation for this discrepancy is the specific characteristics of our study cohort. By design, our parent study excluded patients with high disease activity. The MEX-SLEDAI scores in our population were clustered at the lower end of the scale. It is conceivable that the pathogenic contribution of TNF−α becomes more pronounced and systemically detectable only during periods of high disease activity or flares. This is proven by the pivotal involvement of TNF-α in macrophage

activation syndrome (MAS) in systemic lupus erythematosus (SLE). Macrophage activation syndrome (MAS) is a critical complication marked by liver failure, hepatosplenomegaly, coagulopathy, pancytopenia, and elevated temperature. The most common triggers are infections and SLE flares. The. Of all the cytokines, TNF-α is the most significant cytokine in this syndrome. A study comparing cytokine levels in SLE patients with and without MAS showed the significance of this cytokine, revealing elevated levels of TNF-α in comparison to controls. This occurrence underscores the significance of TNF-α in SLE, with its levels potentially influencing the severity or activity of the condition.[18]

This study has several limitations. First, its cross-sectional design prevents any inference of causality. Secondly, our results may lack broader applicability owing to the single-center design and very limited sample size. Third, this disease spectrum was relatively narrow, with most participants presenting with mild activity (median MEX-SLEDAI = 3), while patients with severe disease were excluded by design. These factors restrict the generalizability of our conclusions, as the role of TNF-α may be more evident in severe or organ-threatening disease. A longitudinal study including patients across the full spectrum of disease activity would be necessary to fully elucidate the role of TNF−α as a disease activity biomarker.

5. Conclusion

In conclusion, within our cohort of SLE patients at Dr. Mohammad Hoesin Hospital who presented with mild-to-moderate disease activity, serum TNF−α levels did not serve as a reliable biomarker correlating with clinical activity assessed by MEX-SLEDAI. This highlights that the utility of TNF−α as a biomarker in SLE is likely dependent on the severity of the disease. Future research should focus on longitudinal studies in diverse patient populations, including those experiencing disease flares, to better define the role of this complex cytokine in SLE.

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