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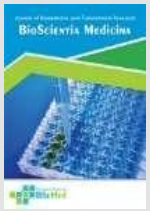

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The Paradoxical Role of Interleukin-10 in Systemic Lupus Erythematosus: A Correlational Study of Serum Levels and Disease Activity

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A B S T R A C T

Background: Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disease where the cytokine Interleukin-10 (IL-10) exhibits a paradoxical role, functioning as both a potent anti-inflammatory mediator and a robust B-cell stimulator. The clinical significance of serum IL-10 as a biomarker of disease activity is a subject of intense debate, with conflicting reports in the literature. This study was designed to investigate this relationship within a specific Southeast Asian cohort. **Methods:** An observational, cross-sectional study was conducted at a tertiary referral hospital in Palembang, Indonesia, enrolling 48 adult patients with a confirmed diagnosis of SLE. Disease activity was quantitatively scored using the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI). Serum IL-10 concentrations were precisely measured using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA). The primary statistical analysis involved the Spearman rank correlation test. A post-hoc power analysis was performed to contextualize the statistical findings. **Results:** The study population was predominantly female (95.8%), with the largest subgroup (54.2%) presenting with mild disease activity. The mean serum IL-10 concentration was 9.91±1.36 pg/mL in the mild activity group, rose to a peak of 12.22±1.95 pg/mL in the moderate activity group, and was 10.65±2.34 pg/mL in the severe activity group. The Spearman correlation test identified a weak, positive association that did not achieve statistical significance (r=0.274, p=0.059). The post-hoc power analysis confirmed the study was underpowered to definitively detect a correlation of this magnitude. **Conclusion:** In this cohort of Indonesian SLE patients, a statistically significant correlation between serum IL-10 levels and disease activity was not established. Given the study's methodological context, including its cross-sectional design and limited statistical power, the findings are inconclusive but hypothesis-generating. The results reinforce the profound complexity of IL-10 biology in SLE and underscore the challenges in validating it as a standalone biomarker, highlighting the need for larger, longitudinal investigations.

1. Introduction

Systemic lupus erythematosus (SLE) stands as a paradigm of systemic autoimmune disease, a chronic and debilitating condition born from a fundamental breach in immunological tolerance to self-antigens.[1] This failure of immune regulation unleashes a cascade of pathogenic events, most notably the production of a wide spectrum of autoantibodies targeting nuclear

components. The ensuing formation of immune complexes, their deposition in microvasculature, and the activation of the complement system precipitate a state of chronic, multisystem inflammation.[2] Consequently, SLE can inflict damage upon virtually any organ system, with the skin, joints, kidneys, blood cells, and central nervous system being common targets. The clinical course of SLE is notoriously unpredictable, characterized by periods of relative quiescence punctuated by debilitating flares of disease activity.[3] This immense heterogeneity in clinical presentation and disease trajectory presents profound challenges for timely diagnosis, effective therapeutic management, and accurate long-term prognostication. The etiology of SLE remains incompletely understood but is recognized as a multifactorial process involving a complex tapestry of genetic susceptibility loci, epigenetic dysregulation, hormonal factors, and a variety of environmental insults that collectively conspire to disrupt immune homeostasis.[4]

The immunological landscape of SLE is dominated by a profound dysregulation of the intricate cytokine network that governs immune cell communication and function.[5] The delicate equilibrium between pro-inflammatory signals that drive immune responses and anti-inflammatory signals that resolve them is lost, leading to a sustained autoimmune assault.[6] Within this disordered milieu, the cytokine Interleukin-10 (IL-10) holds a position of unique complexity and profound paradox. Initially discovered as a cytokine synthesis inhibitory factor produced by T helper 2 (Th2) cells, IL-10 is a pleiotropic molecule celebrated for its potent immunosuppressive capacities. It exerts powerful anti-inflammatory effects by inhibiting the function of key antigen-presenting cells (APCs), such as macrophages and dendritic cells. It achieves this by downregulating the surface expression of Major Histocompatibility Complex (MHC) class II and co-stimulatory molecules, thereby impairing their ability to activate autoreactive T cells. Furthermore, IL-10 directly suppresses the production of a host of critical pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Interleukin-12 (IL-12), which are all major drivers of inflammation in SLE.[7] Through these mechanisms, IL-10 is a cornerstone of immune regulation, essential for maintaining self-tolerance and preventing pathological inflammation.

However, the established anti-inflammatory narrative of IL-10 is sharply contradicted by its actions within the context of SLE. In stark opposition to its immunosuppressive roles, IL-10 is also a potent survival and differentiation factor for B lymphocytes.[8] It promotes B-cell proliferation, maturation into antibody-secreting plasma cells, and immunoglobulin class switching. In a disease fundamentally driven by the production of pathogenic autoantibodies, this potent B-cell-stimulatory function implicates IL-10 as a direct contributor to SLE pathology. This functional dichotomy—acting as both a suppressor of T-cell-mediated inflammation and a promoter of B-cell humoral autoimmunity—places IL-10 at the center of a long-standing scientific controversy. Many investigations have documented elevated serum levels of IL-10 in SLE patients, often correlating with active disease, which supports its pathogenic role.[9] Yet, an almost equal number of studies have reported conflicting results, showing no significant association or even an inverse relationship, leading to the alternative hypothesis that elevated IL-10 may represent a compensatory, albeit insufficient, counter-regulatory feedback mechanism aimed at dampening the systemic inflammation.

The precise monitoring of disease activity is indispensable for the modern management of SLE. It allows clinicians to tailor immunosuppressive therapy, aiming to control inflammation and prevent irreversible organ damage while minimizing treatment-related toxicity. To this end, validated clinical instruments like the systemic lupus erythematosus disease activity index (SLEDAI) and its widely used variant, the Mexican SLEDAI (MEX-SLEDAI), have been developed. These scoring systems provide a standardized framework for quantifying

disease activity across various organ systems. While invaluable, these tools rely on a composite of clinical signs and laboratory tests and may not fully reflect the dynamic immunological processes underlying the disease state. This has fueled a relentless search for sensitive and specific biological markers that can provide an objective measure of disease activity, predict impending flares, and serve as surrogate endpoints in clinical trials. The deeply conflicting evidence surrounding IL-10's association with SLE activity highlights the critical need for further research, especially in patient populations that have been historically underrepresented in immunological studies.[10] It is well-established that genetic ancestry and regional environmental factors can substantially shape the immune system and cytokine profiles. The majority of research into SLE biomarkers has been conducted in cohorts of European, North American, and East Asian descent. Comprehensive data from Southeast Asian populations, such as that of Indonesia, are conspicuously limited. Evaluating these immunologic relationships in diverse ethnic groups is paramount for a more complete and global understanding of SLE and for validating biomarkers that can be applied across different patient populations.

The novelty of this investigation is rooted in its dedicated focus on elucidating the complex relationship between serum IL-10 and disease activity within a specific and understudied Indonesian patient cohort. By applying the rigorously validated MEX-SLEDAI instrument in this distinct population, our research furnishes crucial regional data, enriching the global tapestry of SLE immunopathogenesis. This study directly confronts the prevailing controversy over the role of IL-10 by testing its correlation with clinical disease severity in a population possessing a unique genetic architecture and set of environmental exposures, thus providing a fresh perspective on this enduring immunological paradox. Given the existing knowledge gap, the primary aim of this study was to meticulously analyze and quantify the correlation between the serum concentration of Interleukin-10 and the degree of clinical disease activity, as measured by the MEX-SLEDAI score, among patients diagnosed with systemic lupus erythematosus at a major tertiary care hospital in Palembang, Indonesia. Through this investigation, we sought to critically assess the potential clinical utility of serum IL-10 as a viable biomarker of disease activity in this specific demographic and to contribute substantive evidence toward resolving the ongoing scientific debate surrounding its enigmatic and paradoxical functions in SLE.

2. Methods

This research was structured as an observational, analytical study implementing a cross-sectional design to investigate the association between variables at a single point in time. This design was chosen for its feasibility in a clinical setting and its utility for hypothesis generation regarding potential biomarker associations. The study was conducted at the Dr. Mohammad Hoesin General Hospital located in Palembang, the capital of South Sumatra, Indonesia. This institution functions as a premier tertiary referral hospital and academic medical center for the region. Participants were recruited from both the inpatient services and the specialized outpatient clinics of the Allergy-Immunology and Rheumatology divisions within the Department of Internal Medicine. The period designated for patient enrollment, data collection, and acquisition of biological specimens spanned from September 2024 to November 2024. The study protocol was rigorously reviewed and granted full ethical clearance by the Health Research Ethics Committee (KEPK) of the Dr. Mohammad Hoesin General Hospital (Reference No. DP.04.03/D.XVIII.6.8/ETIK/178/2024), ensuring adherence to national and international ethical guidelines for research involving human subjects.

The target population for this study encompassed all patients with an established diagnosis of SLE who were receiving ongoing medical care at the study institution. The accessible population consisted of all SLE patients who presented to the designated

inpatient wards or outpatient clinics during the defined three-month study timeframe. A consecutive sampling strategy was utilized to recruit participants. This non-probability sampling method involves enrolling every patient who meets the predetermined eligibility criteria in the order they present, continuing until the pre-calculated minimum sample size for statistical power was achieved.

Inclusion Criteria: Patients with a definitive diagnosis of SLE, confirmed according to the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria; Patients aged 18 years or older at the time of enrollment; Patients who demonstrated a clear understanding of the study's objectives and procedures and voluntarily provided written informed consent to participate. Exclusion Criteria: Patients diagnosed with other significant systemic autoimmune diseases (such as Rheumatoid Arthritis or Systemic Sclerosis) or immunodeficiency conditions (such as Human Immunodeficiency Virus [HIV] infection), to prevent the confounding influence of other immunological pathologies on cytokine measurements; Patients who were pregnant or currently breastfeeding, due to the profound physiological and immunological changes associated with these states; Patients using hormonal contraceptives, to avoid potential modulation of the immune system by exogenous hormones; Patients presenting with clinical signs and symptoms suggestive of an active, acute infection at the time of evaluation, as infections can independently and dramatically alter cytokine levels; Patients whose disease was classified as being in a state of clinical remission, defined as a MEX-SLEDAI score of 0 or 1, as the study's primary objective was to investigate the correlation with active disease; Patients who, after being provided with a full explanation of the study, declined to participate.

Following the informed consent process, each enrolled participant underwent a systematic and comprehensive evaluation performed by the principal investigator. All data were meticulously recorded on a standardized case report form designed specifically for this study. The collected data included: Demographic Profile: Detailed information on age, gender, highest attained level of education, and current occupation was recorded; Clinical History and Treatment: This included the duration since the initial SLE diagnosis, the total duration of immunosuppressive treatment, and a detailed list of current medications. Specific attention was given to the number of immunosuppressive agents being used and the exact daily dosage of methylprednisolone or its equivalent. The presence and nature of any comorbid conditions, such as hypertension, diabetes mellitus, or chronic kidney disease, were also documented; Anthropometric Data: Standardized measurements of height (in meters) and weight (in kilograms) were taken to calculate the Body Mass Index (BMI, kg/m^2). Patients were then categorized as underweight, normal weight, overweight, or obese based on the Asia-Pacific classification guidelines from the World Health Organization; Disease Activity Assessment: A comprehensive clinical examination and review of recent laboratory results were conducted to facilitate the scoring of disease activity.

The degree of SLE disease activity for each participant at the moment of enrollment was quantitatively evaluated using the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI). The MEX-SLEDAI is a well-validated and widely used clinical index that assesses disease activity based on the presence of 12 specific clinical and laboratory manifestations within the preceding 28 days. Each item is assigned a weighted score, and the total score can range from 0 to 36, with higher scores indicating greater disease activity. For the purpose of statistical analysis, patients were stratified into three distinct categories of active disease based on their total MEX-SLEDAI score: Mild Activity: MEX-SLEDAI score of 2–5; Moderate Activity: MEX-SLEDAI score of 6–9; Severe Activity: MEX-SLEDAI score of ≥10. To ensure the reliability and consistency of the scoring, all assessments were performed by the trained principal investigator under the direct supervision of

senior consultants in the fields of Allergy-Immunology and Rheumatology.

A single 7 mL sample of venous blood was drawn from each participant using standard phlebotomy techniques under strict aseptic conditions. This sample was then partitioned for different analyses. A portion was used for routine laboratory evaluations relevant to the MEX-SLEDAI scoring, including a complete blood count, renal function tests, and urinalysis. The remaining 5 mL was specifically designated for the measurement of serum IL-10. This portion was collected into a plain tube without an anticoagulant. The blood was allowed to clot at room temperature for approximately two hours, followed by centrifugation for 12 minutes to separate the serum from the cellular components. The clear serum supernatant was then carefully aspirated, divided into aliquots, and immediately transferred to a freezer for storage at −80°C. This ultra-low temperature storage was maintained until the day of the assay to preserve the integrity of the cytokine. The concentration of IL-10 in the thawed serum samples was precisely quantified using a commercial quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit. The assay was performed in strict accordance with the detailed protocol provided by the manufacturer. To minimize potential inter-assay variability and ensure the consistency of results, all patient samples were analyzed together in a single batch on the same day. The optical density was read using a microplate reader, and concentrations were calculated based on a standard curve. The final concentration of IL-10 for each sample was reported in picograms per milliliter (pg/mL).

All data were compiled and subjected to statistical analysis using the SPSS (Statistical Package for the Social Sciences) software, version 27 for Windows. The initial step involved descriptive analysis to summarize the baseline demographic and clinical characteristics of the study cohort. Categorical variables were presented as absolute frequencies and relative percentages. The distribution of numerical data, specifically the serum IL-10 levels, was assessed for normality using the Shapiro-Wilk test, which is appropriate for the study's sample size. The primary analytical objective was to determine the correlation between the serum IL-10 level (a numerical variable) and the disease activity category (an ordinal variable). The Spearman rank correlation test, a non-parametric measure of rank correlation, was chosen as the appropriate statistical test for this analysis. The resulting Spearman's correlation coefficient (r) was used to quantify the strength and direction of the monotonic relationship, while the associated p-value was used to assess its statistical significance. A two-tailed p-value of less than 0.05 was prospectively defined as the threshold for statistical significance. As a secondary analysis, unpaired t-tests were conducted to compare the mean IL-10 levels between the different pairs of disease activity groups (mild versus moderate, mild versus severe, and moderate versus severe). To visually illustrate the relationship between the primary variables, a scatter plot was constructed, displaying individual patient IL-10 levels against their respective disease activity categories.

3. Results

Figure 1 provides a comprehensive schematic overview of the key demographic characteristics of the 48 adult systemic lupus erythematosus (SLE) patients enrolled in this study, meticulously stratified by their level of disease activity. The most striking feature, immediately apparent from the Sex Distribution panel, is the profound female predominance, a well-established hallmark of SLE epidemiology. Across all levels of disease activity, female patients constitute the overwhelming majority. Of the 46 female patients, 25 (54.3%) presented with mild disease, 10 (21.7%) with moderate, and 11 (23.9%) with severe disease. This distribution underscores that the burden of active lupus, regardless of severity, is disproportionately borne by women in this cohort. The male cohort, while very small (n=2), was split between the mild and severe activity groups, precluding any meaningful statistical comparison but visually reinforcing the rarity of the disease in males. The Age Distribution panel further

refines the population profile, revealing that the disease predominantly affects individuals in their prime productive years. The 20-44 years age bracket represents the largest segment across all activity levels, containing 20 patients with mild, 8 with moderate, and 10 with severe disease. This concentration highlights the significant socioeconomic and personal impact of SLE, as it most affects adults during their key family-building and career-developing years. Younger patients (<20 years) and older patients (≥45 years) were present in smaller numbers and were distributed across the different activity strata, suggesting that while SLE is most common in young adulthood, it can manifest with varying severity at any age. Turning to socioeconomic indicators, the Education by Activity Level chart demonstrates that the majority of patients in the study, irrespective of their disease activity, had an educational attainment of high school or less. This demographic characteristic is particularly prominent in the mild activity group, where 23 patients fall into this category. Similarly, the Occupation by Activity Level panel shows that "Housewife" was the most common occupational status reported, with 12 individuals in the mild, 6 in the moderate, and 8 in the severe activity groups. Together, these findings provide a valuable glimpse into the socioeconomic context of the study population, suggesting that SLE in this region affects a broad cross-section of society. Figure 1 effectively illustrates that the study cohort is representative of the classic SLE demographic profile: predominantly female and affecting young to middle-aged adults. The visual stratification by disease activity shows that these core demographic features are consistent across the spectrum of disease severity, from mild to severe manifestations. This detailed demographic foundation is essential for the interpretation of the clinical and immunological data that follow, ensuring that the findings are understood within the specific context of this well-characterized Indonesian patient population.

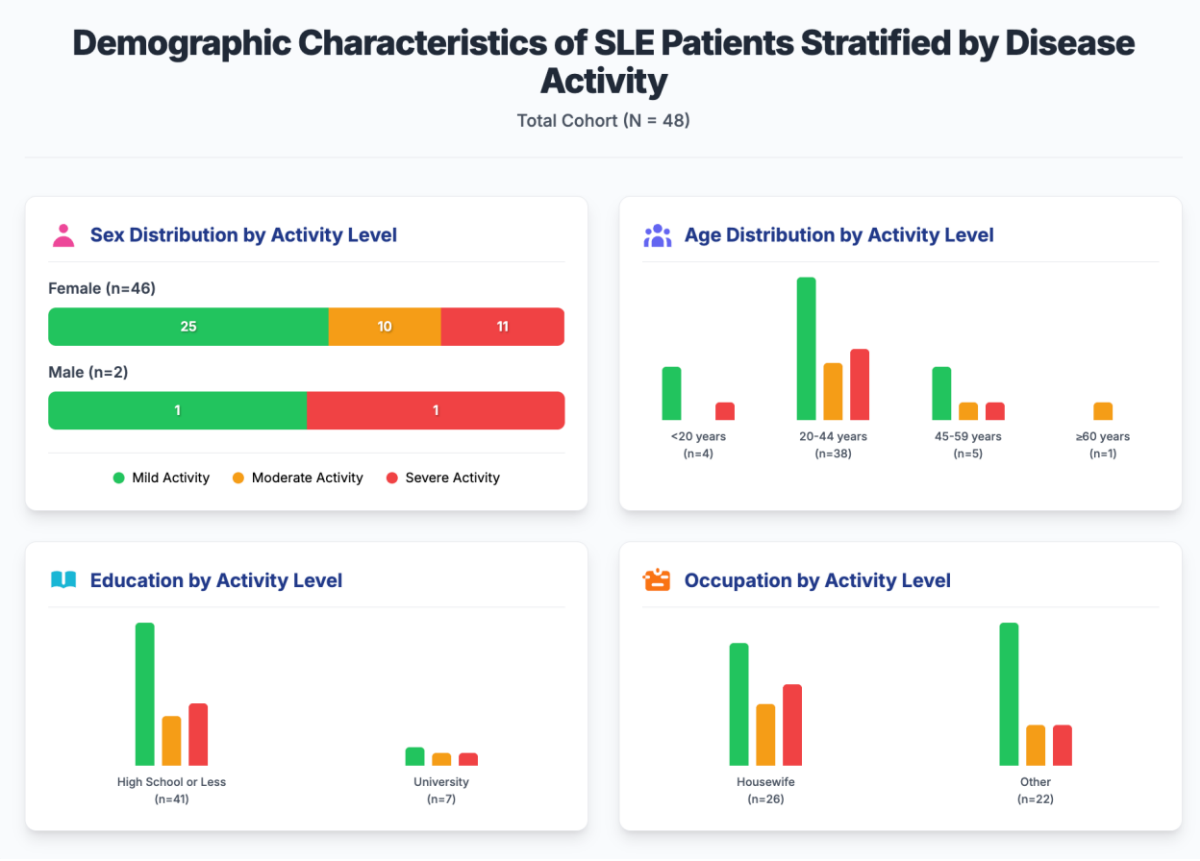

Figure 1. Demographic characteristics of SLE patients stratified by disease activity.

Figure 2 provides a detailed and multi-faceted visualization of the core clinical characteristics of the 48-patient SLE cohort, offering critical insights into the therapeutic and health status of these individuals as stratified by disease activity. The Treatment Duration panel, creatively visualized using partitioned capsules, reveals an interesting dynamic between disease chronicity and activity at the time of assessment. While a majority of patients in the mild activity group (69.2%) had been receiving treatment for over a year, suggesting a state of managed, long-standing disease, the inverse was true for the moderate activity group, where 60% of patients had a treatment duration of one year or less. The severe group was evenly split. This pattern suggests that patients with more recent diagnoses or shorter treatment histories may be more likely to present with moderate-to-severe disease activity, a clinically intuitive finding that underscores the challenge of achieving initial disease control. Examining the therapeutic complexity in the Number of Immunosuppressants panel provides further nuance. The proportion bars clearly illustrate that the majority of patients across all activity levels were on multi-drug regimens, typically involving two or three immunosuppressive agents. Notably, even in the mild activity group, 76.9% of patients required two or more agents to maintain their low disease activity state. This is a crucial clinical insight, indicating that "mild" disease in this cohort does not equate to simple or minimal therapy. Instead, it suggests that a significant level of immunomodulation is necessary to keep the disease in check, reflecting the inherent severity and complexity of SLE even when clinical manifestations are limited. The Daily Glucocorticoid Dose section, depicted through elegant donut charts, visualizes the steroid burden across the groups. As expected, there is a clear trend towards higher steroid doses with increasing disease activity. While over half of the patients in the mild group were on low-dose maintenance therapy (<7.5 mg/day), the proportion of patients requiring higher doses (≥7.5 mg/day) or who were not on steroids at all increased in the moderate and, most dramatically, the severe activity groups. This reflects standard clinical practice, where glucocorticoids are a primary tool for managing flares, but it also highlights the significant treatment burden associated with more active disease. Finally, the Presence of Comorbidities panel, represented by a compelling radial chart, speaks to the systemic impact of SLE on overall patient health. The data show a clear and concerning trend: the prevalence of having at least one comorbidity rises substantially with disease activity, from 19.2% in the mild group to 40.0% in the moderate group, and remaining high at 33.3% in the severe group. This finding powerfully illustrates that higher SLE activity is associated with a greater overall health burden, reinforcing the concept that lupus is not just an immunological disorder but a systemic condition with far-reaching consequences for patient well-being. Figure 2 masterfully dissects the clinical landscape of the study cohort. It portrays a population facing significant therapeutic challenges, where even mild disease requires complex treatment regimens. The data strongly suggest that increasing disease activity is associated with more recent disease onset, a greater reliance on high-dose glucocorticoids, and a higher burden of comorbid conditions, providing an essential clinical framework for the interpretation of the study's core immunological findings.

Figure 3 provides a powerful and multi-faceted visual summary of the core findings from this investigation into the relationship between serum Interleukin-10 (IL-10) and disease activity in a cohort of 48 patients with Systemic Lupus Erythematosus (SLE). The primary analysis yielded a Spearman's correlation coefficient (r) of 0.274, indicating a weak positive association between rising IL-10 levels and increasing disease severity. However, this trend did not achieve statistical significance, as evidenced by the p-value of 0.059. This borderline result is the central finding of the study and speaks to the complex, non-linear nature of IL-10 in SLE. The adjacent box-and-whisker plot provides a granular view of the data distribution that helps to explain this statistical ambiguity. It clearly shows a non-linear pattern: the

median IL-10 level is lowest in the mild activity group, peaks in the moderate activity group, and then decreases in the severe activity group. This plot, which also precisely displays the mean, median, and full data range for each category, visually confirms that IL-10 does not increase in a simple, linear fashion with disease activity. The accompanying table provides the exact numerical values for these metrics, offering a complete and transparent summary of the data. This scatter plot is perhaps the most compelling illustration of the study's main conclusion. It reveals a dramatic vertical spread and considerable overlap of data points across the three activity groups. One can immediately observe patients with mild disease who have IL-10 levels as high as some patients with severe disease, and vice versa. This extensive overlap is the statistical reality that underlies the weak correlation coefficient and the non-significant p-value. The faint, gently sloping trendline visually represents the weak positive association, but the dispersion of the individual data points around this line is the dominant feature. The plot powerfully communicates that while a subtle trend may exist, an individual patient's IL-10 level is a poor predictor of their specific disease activity category. Figure 3 masterfully integrates the study's key findings into a single, cohesive narrative. It moves beyond a simple statement of statistical significance to provide a rich, multi-layered view of the data. The figure clearly communicates the main takeaway: while there is a hint of a positive association between serum IL-10 and SLE disease activity, the relationship is weak, non-linear, and characterized by extensive overlap between individuals. This visual evidence strongly supports the conclusion that serum IL-10, when measured as a single analyte in a cross-sectional manner, lacks the discriminatory power to serve as a reliable standalone biomarker for disease activity in this patient population.

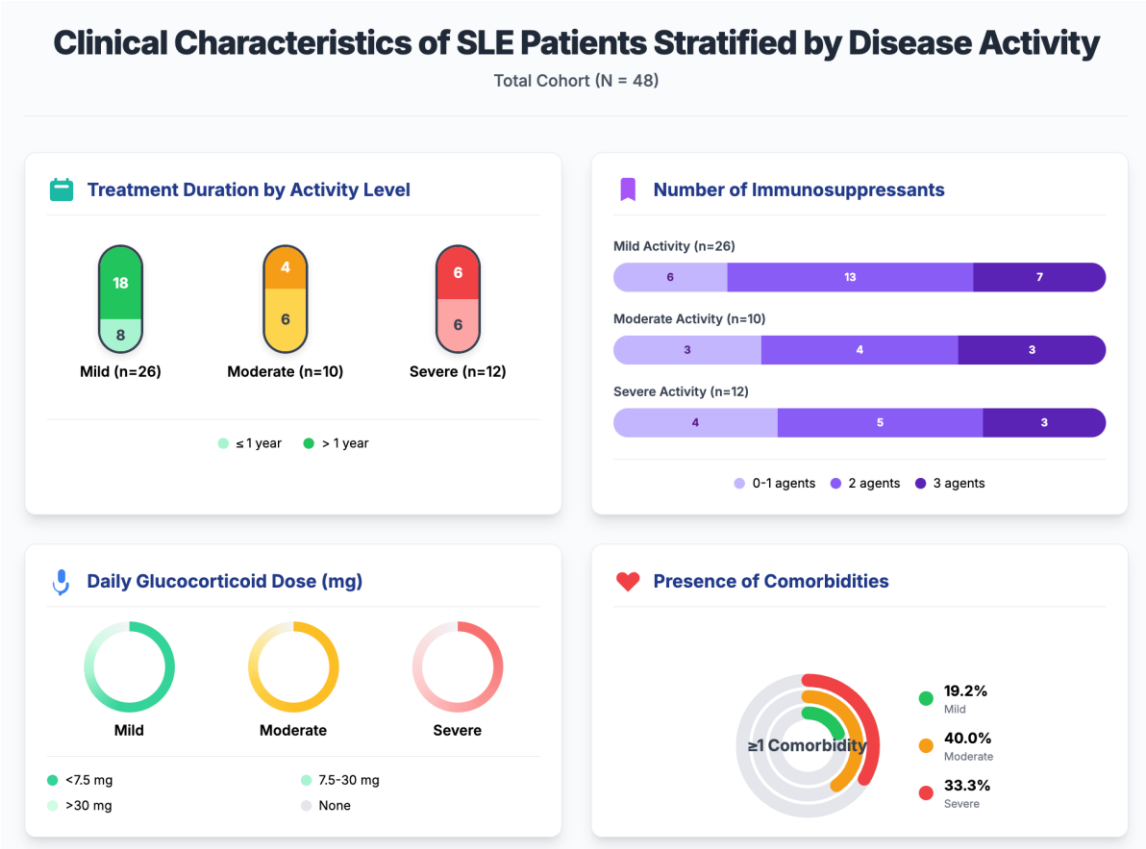

Figure 2. Clinical characteristics of SLE patients stratified by disease activity.

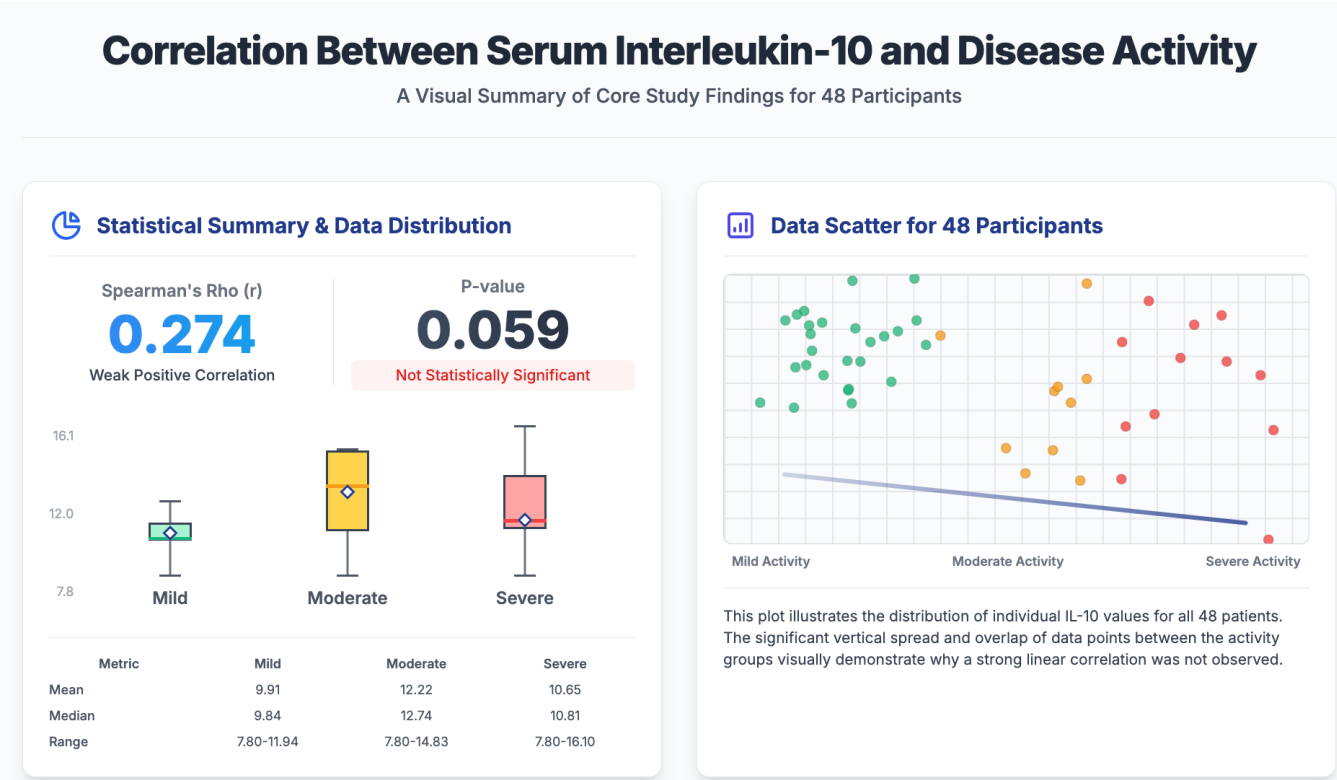

Figure 3. Correlation between serum interleukin-10 and disease activity.

4. Discussion

The investigation into the role of Interleukin-10 (IL-10) in the pathophysiology of systemic lupus erythematosus (SLE) is fraught with complexity, reflecting the cytokine's deeply paradoxical biological functions.[11] This study was conceived to add a crucial piece to this intricate puzzle by examining the correlation between serum IL-10 concentrations and clinical disease activity within a unique Indonesian cohort. The cardinal finding of our research is the absence of a statistically significant linear correlation between these two variables.[12] With a Spearman correlation coefficient (r) of 0.274 and a p-value of 0.059, our results, while indicating a weak positive trend, ultimately suggest that in this patient population, a single measurement of serum IL-10 does not serve as a robust, independent biomarker of disease severity as quantified by the MEX-SLEDAI score. This borderline-significant result is not merely a negative finding; rather, it is a powerful affirmation of the multifaceted and non-linear nature of IL-10 in the broader context of SLE immunopathogenesis. Our finding of a non-significant correlation is consistent with a segment of the existing literature, which has similarly struggled to establish a simple, direct relationship between IL-10 and SLE activity. The failure to find a strong linear association can be rationalized by dissecting the dual, and often opposing, pathophysiological roles of IL-10. On one hand, IL-10 is a potent pro-inflammatory driver of humoral immunity. It is a critical factor for the survival, proliferation, and differentiation of B lymphocytes into autoantibody-secreting plasma cells.[13] This function directly feeds into the core pathogenic mechanism of SLE: the production of autoantibodies that form damaging immune complexes. This pro-B cell activity provides a strong theoretical basis for why IL-10 levels might be expected to rise with increasing disease activity. Our data partially support this, as the mean IL-10 levels in

both the moderate and severe activity groups were indeed higher than in the mild activity group. The weak positive trend (r=0.274) likely reflects this underlying pathogenic contribution.

On the other hand, IL-10 is a master anti-inflammatory cytokine. It is the principal effector molecule for several types of regulatory cells, including regulatory T cells (Tregs) and regulatory B cells (Bregs).[14] Its canonical function is to suppress immune responses by inhibiting antigen presentation by myeloid cells and by limiting the production of pro-inflammatory cytokines from T helper 1 (Th1) and T helper 17 (Th17) cells. In the context of the raging systemic inflammation that defines active SLE, it is plausible that the immune system mounts a compensatory, counter-regulatory surge in IL-10 production in an attempt to restore homeostasis and limit tissue damage. Therefore, the total measured serum IL-10 at any given moment is not a pure reflection of a single pathogenic process. Instead, it represents a composite signal—an algebraic sum of the pathogenic, B-cell-driving IL-10 and the protective, counter-regulatory IL-10.[15] This inherent biological duality, a molecular "tug-of-war," provides a compelling pathophysiological explanation for why a simple linear correlation with a composite clinical activity score would be weak or absent. The two opposing signals may effectively cancel each other out, leading to an ambiguous and statistically non-significant result.

Perhaps the most thought-provoking aspect of our data is the non-linear, bell-shaped trend observed in mean IL-10 levels, which peaked in the moderately active disease group and was lower in both the mild and severe groups. This pattern may offer a window into the dynamic nature of the immune response as SLE progresses. In a state of low-grade activity, the pathogenic stimuli are relatively contained, and the baseline production of both pathogenic and regulatory IL-10 is low, resulting in the lowest mean levels observed in our study. As the disease escalates from mild to moderate, the inflammatory processes intensify, leading to a significant increase in the production of pathogenic, B-cell-stimulatory IL-10. Concurrently, the immune system recognizes this escalating threat and mounts a robust counter-regulatory response, leading to a surge in protective, anti-inflammatory IL-10. The combination of these two amplified signals results in the peak serum concentrations seen in our moderate activity group. The statistically significant difference in IL-10 levels between the mild and moderate groups strongly supports this concept of an actively engaged and escalating immune battle. The subsequent decrease in mean IL-10 levels in the severe activity group is counterintuitive if one only considers the pro-inflammatory role of IL-10.[16] However, it can be explained by several potential pathophysiological mechanisms. One possibility is a state of regulatory exhaustion. In the face of overwhelming, unremitting inflammation characteristic of severe lupus, the regulatory cells (Tregs and Bregs) may become anergic, apoptotic, or functionally impaired, leading to a collapse of the compensatory anti-inflammatory IL-10 response. Another possibility is a qualitative shift in the cytokine milieu. In severe, life-threatening lupus, other cytokine pathways, particularly the type I interferon system, may become overwhelmingly dominant, altering the transcriptional programs of immune cells and potentially suppressing the IL-10 axis. This non-linear pattern suggests that the utility of IL-10 as a biomarker may be state-dependent and cannot be interpreted without considering the overall disease severity.[17]

Figure 4 presents a conceptual pathophysiological model designed to synthesize the study's core findings and offer a compelling biological explanation for the observed weak, non-linear relationship between serum Interleukin-10 (IL-10) and disease activity in systemic lupus erythematosus (SLE). The first panel, representing Mild Disease Activity, depicts a state of tenuous immunological balance. Here, the "Pathogenic Arm"—representing the forces driving the disease, such as autoreactive B-cell activation—is shown to be at a low level. This subdued pathogenic activity elicits a proportional counter-response from

the "Regulatory Arm," which works to maintain immune suppression. The resulting total serum IL-10, visualized in the central vial, is therefore "Low." This level is understood not as an absence of activity, but as a composite signal reflecting the sum of a small amount of pathogenic, B-cell-driving IL-10 and a corresponding small amount of compensatory, anti-inflammatory IL-10. This state of low-level, balanced activity provides a clear pathophysiological basis for the lowest mean IL-10 levels observed in the study's mild activity group.

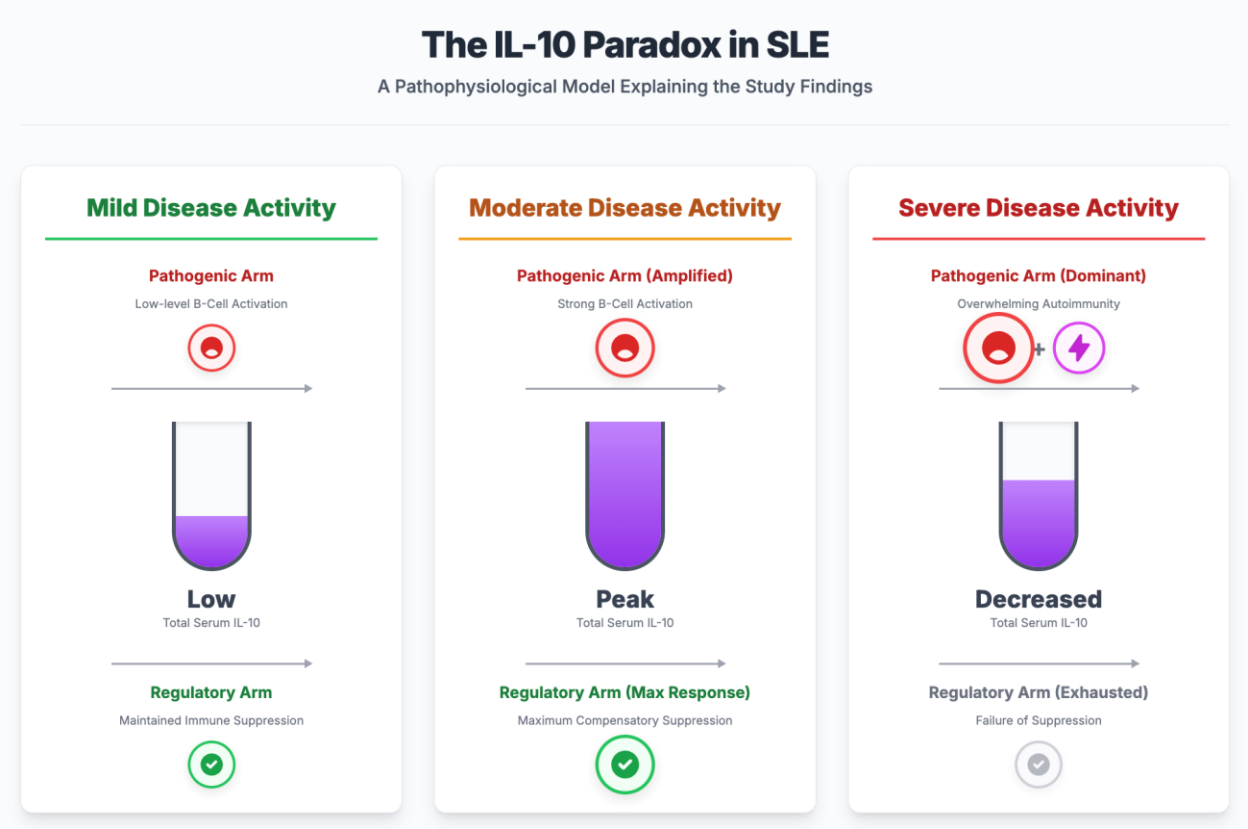

Figure 4. The IL-10 paradox in SLE.

The central panel, illustrating Moderate Disease Activity, is key to understanding the paradox and is portrayed as an "escalating battle." The pathogenic load has significantly increased, as indicated by the amplified icon. In response to this growing threat, the regulatory arm of the immune system mounts a robust, maximal counter-attack, dramatically increasing the production of protective, anti-inflammatory IL-10 in an attempt to restore homeostasis. Critically, the pathogenic processes themselves are also contributing a larger amount of IL-10 to the total pool. The result is a surge in *both* pathogenic and compensatory IL-10, leading to the "Peak" level of total serum IL-10 measured in the vial. This model elegantly explains the counterintuitive but statistically significant peak in IL-10 levels observed in the study's moderate activity group, framing it not as the worst stage of disease, but as the point of most intense immunological conflict. The final panel, depicting severe disease activity, illustrates a state of immunological dysregulation where the balance is irrevocably broken. The "Pathogenic Arm" is now overwhelming and dominant, further amplified by other potent pathways, such as the Type I Interferon

system (represented by the lightning bolt icon).[18] Crucially, the model proposes a state of "Regulatory Exhaustion," where the compensatory systems fail. The regulatory icon is shown as depleted and grayed out, symbolizing the inability of regulatory cells to sustain their anti-inflammatory IL-10 production in the face of relentless inflammation. The result is a paradoxical decrease in the total measured serum IL-10, even as clinical disease activity reaches its zenith. This explains the drop in mean IL-10 levels from the moderate to the severe group in the study's findings. Figure 4 provides a powerful narrative framework. It posits that the measured serum IL-10 in SLE is not a simple linear marker but rather the net sum of a dynamic, two-front war. The weak and non-linear correlation found in the study is a logical consequence of this complex interplay, where the highest levels of IL-10 do not signify the worst disease but rather the most intense phase of the immunological conflict, just before the regulatory systems become overwhelmed. This model provides a clear, scientifically grounded interpretation of the study's nuanced findings.

A fundamental limitation of our study, and indeed of most studies in this field, is the measurement of total serum IL-10 without identifying its cellular origin. The functional consequence of IL-10 is highly dependent on which cell type is producing it, in which microenvironment, and at what time.[19] For instance, IL-10 produced by a Breg in a lymph node may exert a powerful suppressive effect on an adjacent autoreactive T cell. In contrast, IL-10 produced by an extrafollicular T helper cell might primarily act to drive the differentiation of a nearby autoantigen-specific B cell into a pathogenic plasma cell. The circulating serum level is a crude integration of all these localized and functionally distinct events. The inability to distinguish between "good" (regulatory) and "bad" (pathogenic) IL-10 is a major confounding factor that further explains the weak and ambiguous correlation with the clinical phenotype. Furthermore, the results must be considered within the context of our specific Indonesian cohort. The genetic regulation of cytokine production is known to vary significantly across different ethnic populations due to the differential prevalence of single-nucleotide polymorphisms (SNPs) in cytokine gene promoters and regulatory regions. Polymorphisms in the IL-10 gene are well-documented to influence its expression levels. It is therefore conceivable that the genetic background of the Indonesian population leads to a distinct pattern of IL-10 regulation and response compared to the European or East Asian populations, where much of the previous research has been conducted.[20] This underscores the critical importance of conducting such immunological studies in diverse global populations to build a truly comprehensive understanding of SLE. Our study contributes a valuable and necessary data point from a region that remains underrepresented in the global SLE research landscape. While this study emphasizes the complexities that challenge the use of IL-10 as a standalone biomarker, it does not diminish its central importance in SLE pathogenesis. The borderline p-value and the clear elevation of IL-10 in active disease states (moderate and severe) compared to mild disease strongly suggest that IL-10 is biologically relevant. This study possesses certain limitations, primarily its cross-sectional design and relatively modest sample size, which precluded the detection of a weaker statistical association and limited the generalizability of the findings. Nevertheless, the strength of the study lies in its use of a validated activity index and its novel contribution of data from a specific Southeast Asian population, thereby addressing a significant gap in the literature and reinforcing the universal complexity of the role of IL-10 in systemic lupus erythematosus.

5. Conclusion

This comprehensive investigation conducted within a cohort of adult Indonesian patients with systemic lupus erythematosus did not find a statistically significant linear correlation between the concentration of serum Interleukin-10 and the degree of clinical disease activity as quantified by the MEX-SLEDAI score. The observed weak positive trend and non-linear pattern, with a peak in moderately active disease, highlight the profound complexity of IL-10

biology. These findings strongly support the prevailing view of IL-10 as a cytokine with a paradoxical and dualistic role in SLE, participating in both pathogenic pro-B-cell pathways and compensatory anti-inflammatory responses. Consequently, a single, static measurement of total serum IL-10 appears to be an unreliable standalone biomarker for accurately gauging disease severity in this patient population. The results from this study underscore the necessity of moving beyond single-cytokine analyses and towards more integrated approaches, such as longitudinal monitoring and the use of multi-cytokine panels, to truly decipher the intricate immunological symphony that orchestrates this enigmatic disease.

6. References

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