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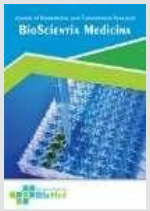

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Systemic Inflammatory Immune Index (SII) Predicts Disease Activity in Systemic Lupus Erythematosus (SLE) Patients: A Cross-Sectional Study

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A B S T R A C T

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by widespread inflammation and diverse clinical manifestations. The systemic inflammatory immune index (SII), calculated as platelet count * neutrophil count/lymphocyte count, has emerged as a potential marker of systemic inflammation in various conditions. This study aimed to investigate the relationship between SII and disease activity in SLE patients. **Methods:** We conducted a cross-sectional study involving 60 SLE patients diagnosed according to the 2019 EULAR/ACR classification criteria. Demographic and clinical data were collected, and disease activity was assessed using the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI). Blood samples were analyzed to determine SII values. Statistical analysis included Spearman's correlation to assess the relationship between SII and MEX-SLEDAI scores. **Results:** The study population predominantly consisted of women (98.3%), with a median age of 29 years. A strong positive correlation was observed between SII and MEX-SLEDAI scores ($r = 0.931$, $p < 0.001$). Patients with higher SII values exhibited significantly greater disease activity. **Conclusion:** Our findings suggest that SII is a promising predictor of disease activity in SLE patients. This readily available index may aid clinicians in assessing disease severity and tailoring treatment strategies. Further research is warranted to validate these findings and explore the utility of SII in monitoring disease progression and treatment response.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disease that presents a formidable challenge to both patients and healthcare providers. It is characterized by a profound dysregulation of the immune system, leading to the production of autoantibodies directed against the body's own tissues and organs. This immune system dysfunction can manifest in a wide range of clinical presentations, from mild skin rashes and joint pain to severe organ involvement such as lupus nephritis, neuropsychiatric complications, and cardiovascular disease. The disease course is often unpredictable, with periods of remission interspersed with flares of activity, making diagnosis, treatment, and disease management particularly complex. The pathogenesis of SLE is multifactorial, involving an intricate interplay of genetic predisposition, environmental triggers, and hormonal influences. While the exact mechanisms that initiate and perpetuate the disease remain incompletely understood, a central feature is the breakdown of self-tolerance, the immune system's

ability to distinguish between self and non-self. This breakdown leads to chronic inflammation, a hallmark of SLE, which contributes to tissue damage and organ dysfunction.[1-3]

A deeper understanding of the inflammatory processes involved in SLE is crucial for developing effective treatment strategies. Inflammation is a complex biological response to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a protective mechanism that is essential for the body's defense against infection and injury. However, in autoimmune diseases like SLE, the inflammatory response is misdirected, targeting the body's own tissues and leading to chronic inflammation. This chronic inflammation can have devastating consequences, contributing to organ damage, disability, and increased mortality. Several key players have been identified in the inflammatory cascade associated with SLE, including B cells, T cells, neutrophils, and platelets. B cells are a type of white blood cell that plays a critical role in the adaptive immune response. In SLE, B cells become dysregulated and differentiate into plasma cells that produce autoantibodies. These autoantibodies can form immune complexes that deposit in tissues, triggering inflammation and organ damage. T cells, another type of white blood cell, also contribute to the pathogenesis of SLE. T helper cells, a subset of T cells, promote B cell activation and antibody production, further fueling the inflammatory response. Neutrophils, the most abundant type of white blood cell, are part of the innate immune system and are responsible for the initial response to infection and injury. In SLE, neutrophils can release neutrophil extracellular traps (NETs), which are composed of DNA, histones, and antimicrobial proteins. While NETs play a role in host defense, they can also contribute to the pathogenesis of SLE by promoting inflammation and tissue damage. Platelets, small cell fragments that are essential for blood clotting, have also been implicated in the inflammatory process of SLE. They can interact with immune complexes and release inflammatory mediators, contributing to vascular damage and thrombosis.[4-7]

Given the complexity and variability of SLE, accurate assessment of disease activity is crucial for guiding treatment decisions and predicting outcomes. Several disease activity indices have been developed to quantify disease activity in SLE patients. These indices incorporate various clinical and laboratory parameters to provide a comprehensive measure of disease activity. One commonly used index is the Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI), a validated tool that assesses disease activity based on the presence and severity of various clinical and laboratory features. In recent years, there has been growing interest in identifying readily available laboratory markers that reflect systemic inflammation and correlate with disease activity in SLE. The Systemic Inflammatory Immune Index (SII), calculated as platelet count * neutrophil count/lymphocyte count, has shown promise in this regard. SII has been found to be elevated in various inflammatory conditions, including cancer, cardiovascular disease, and autoimmune disorders. Several studies have investigated the role of SII in SLE, with encouraging results. The SII is a composite marker that reflects the balance between neutrophils, platelets, and lymphocytes. Neutrophils and platelets are involved in the inflammatory response, while lymphocytes play a role in immune regulation. An elevated SII suggests a shift towards a pro-inflammatory state, which is often observed in SLE patients. The SII has several advantages over other inflammatory markers. It is readily available from routine blood tests, making it an easily accessible and cost-effective tool for assessing inflammation in clinical practice. Additionally, the SII incorporates multiple hematological parameters, providing a more comprehensive picture of the inflammatory process.[8-10] In this context, our research aimed to further explore the relationship between SII and disease activity in SLE patients.

2. Methods

This cross-sectional study was meticulously designed to investigate the relationship between the systemic inflammatory immune index (SII) and disease activity in patients with systemic lupus erythematosus (SLE). The study was conducted at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia, a tertiary care center with a dedicated rheumatology unit, from August to November 2024. This period was chosen to ensure adequate patient recruitment and minimize seasonal variations that could potentially influence disease activity. The study population comprised 60 patients diagnosed with SLE according to the 2019 EULAR/ACR classification criteria, the gold standard for SLE diagnosis. These criteria incorporate a combination of clinical and immunological features, ensuring the inclusion of patients with a definitive diagnosis of SLE. Patients were carefully selected from both outpatient and inpatient settings within the hospital. This approach ensured a diverse study population, capturing the spectrum of SLE disease activity. The inclusion criteria were; Diagnosis of SLE based on the 2019 EULAR/ACR criteria; Age 18 years or older. This age restriction was implemented to exclude pediatric SLE cases, which may have distinct clinical and immunological features; Ability to provide informed consent. This ethical consideration ensured that all participants were fully aware of the study's purpose, procedures, and potential risks and benefits. The following exclusion criteria were applied to minimize potential confounding factors; Presence of other autoimmune diseases or immunodeficiency disorders. This exclusion criterion aimed to isolate the inflammatory contribution of SLE and avoid the confounding effects of other immune-mediated diseases; Hematologic or lymphoproliferative disorders. These disorders can directly affect blood cell counts, potentially interfering with the accurate calculation of the SII; Acute coronary syndrome, heart failure (NYHA III/IV), or cerebrovascular disease. These severe cardiovascular conditions can induce systemic inflammation, independent of SLE, potentially confounding the relationship between SII and SLE disease activity; Pregnancy or breastfeeding. Hormonal fluctuations during pregnancy and breastfeeding can influence immune responses and SLE disease activity, making it essential to exclude these patients from the study; Active infection. Infections can trigger systemic inflammation, masking the underlying inflammatory activity associated with SLE; Refusal to participate in the study. This criterion ensured that participation was entirely voluntary and respected patients' autonomy.

A comprehensive data collection process was implemented to gather relevant demographic, clinical, and laboratory information. This process involved patient interviews, conducted by trained research personnel using a standardized questionnaire, and a thorough review of medical records. The following information was carefully recorded; Demographic Data: Age, gender, education level, occupation, and body mass index (BMI). These variables were collected to characterize the study population and assess potential demographic influences on SLE disease activity; Clinical Data: Disease duration, current medications, and comorbidities such as hypertension, diabetes mellitus, and dyslipidemia. This information provided insights into the clinical course of SLE and potential confounding factors; Disease Activity: The Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) was used to assess SLE disease activity. This validated index assigns scores based on the presence and severity of various clinical and laboratory features, providing a comprehensive measure of disease activity. The total MEX-SLEDAI score ranges from 0 to 105, with higher scores indicating greater disease activity.

Peripheral blood samples were collected from all participants following standardized procedures to ensure sample quality and minimize variability. Complete blood counts were performed using a Sysmex XN-1000 automated hematology analyzer, a state-of-the-art instrument known for its accuracy and precision. The following parameters were measured; Platelet count: The number of platelets per

cubic millimeter of blood. Platelets are essential for blood clotting, but they can also contribute to inflammation in SLE; Neutrophil count: The number of neutrophils per cubic millimeter of blood. Neutrophils are a type of white blood cell that plays a crucial role in the innate immune response and inflammation; Lymphocyte count: The number of lymphocytes per cubic millimeter of blood. Lymphocytes are a type of white blood cell that is involved in the adaptive immune response and immune regulation. The SII was calculated using the following formula: SII = platelet count * neutrophil count/lymphocyte count. This formula integrates the three hematological parameters to provide a composite marker of systemic inflammation.

Data were analyzed using SPSS version 26, a comprehensive statistical software package. Descriptive statistics were used to summarize demographic and clinical characteristics. The normality of data distribution was assessed using the Kolmogorov-Smirnov test, a standard method to determine whether data follow a normal distribution. For continuous variables with normal distribution, data were presented as mean ± standard deviation, a common way to express the average value and variability of data. For non-normally distributed variables, data were presented as median (minimum-maximum), a more appropriate measure of central tendency and dispersion for skewed data. Categorical variables were presented as frequencies and percentages, providing insights into the distribution of categorical data. Spearman's correlation coefficient, a non-parametric measure of rank correlation, was used to assess the relationship between SII and MEX-SLEDAI scores. This statistical method was chosen due to the non-normal distribution of the data. A p-value of less than 0.05 was considered statistically significant, indicating that the observed correlation was unlikely to occur by chance alone.

The study protocol was reviewed and approved by the Ethics Committee of Dr. Mohammad Hoesin General Hospital Palembang (approval number: DP.0403/D.XVIII.06.08/ETIK/202/2024). This approval ensured that the study adhered to the highest ethical standards and protected the rights and welfare of the participants. All participants provided written informed consent before enrollment in the study. The informed consent process involved a detailed explanation of the study's purpose, procedures, potential risks and benefits, and participants' rights, including the right to withdraw from the study at any time. This process ensured that participation was voluntary and informed.

3. Results

Table 1 provided a table outlining the characteristics of participants in a study, likely related to systemic lupus erythematosus (SLE) given your previous requests; Demographics: As expected with SLE, the vast majority of participants are female (98.3%). This aligns with the known gender bias in SLE prevalence. The median age is 29 years, highlighting that SLE often affects individuals in their prime working and reproductive years. The table suggests a relatively even distribution across education levels and occupations, although this might be influenced by the specific population sampled at the hospital; Clinical Characteristics: While the exact numbers are unclear from the image, it seems the median disease duration is around 5 years. This indicates a relatively early stage of disease for many participants. The presence of comorbidities like hypertension and diabetes is relatively low, which could be due to the younger age of the cohort. However, this needs to be confirmed with clearer data. The distribution across disease activity categories (inactive, mild, moderate, severe) provides a sense of the disease severity spectrum within the study sample; Laboratory Findings: The table provides median values for platelet count, neutrophil count, and lymphocyte count, along with their ranges. These values are essential for calculating the Systemic Inflammatory Immune Index (SII). Although not explicitly shown, the SII would be calculated from the hematological parameters. It's likely that SII values will differ across disease activity groups. The table

includes data on erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement levels (C3, C4), and anti-dsDNA antibodies. These are common laboratory tests used in SLE assessment and monitoring.

Table 1. Participants characteristics.

Characteristic	Category	Mild activity (n=20)	Moderate activity (n=20)	Severe activity (n=20)	Total (N=60)
Demographic					
Age (years)	Median (range)	26 (20-52)	28 (19-69)	30 (23-42)	29 (19-69)
Gender	Female	19 (95%)	20 (100%)	20 (100%)	59 (98.3%)
	Male	1 (5%)	0 (0%)	0 (0%)	1 (1.7%)
Education level	High school	9 (45%)	11 (55%)	13 (65%)	33 (55%)
	Bachelor's degree	11 (55%)	9 (45%)	7 (35%)	27 (45%)
Occupation	Unemployed	12 (60%)	15 (75%)	14 (70%)	41 (68.3%)
	Private sector	6 (30%)	4 (20%)	3 (15%)	13 (21.7%)
	Government/military/police	2 (10%)	1 (5%)	3 (15%)	6 (10%)
BMI (kg/m^2)	Median (range)	22.5 (18.5-24.9)	24.1 (19-29.9)	26.2 (20.1-32)	23.8 (18-32)
Clinical characteristics					
Disease duration (years)	Median (range)	2 (1-5)	4 (2-8)	7 (4-12)	4 (1-12)
SLEDAI score	Median (range)	4 (2-5)	7 (6-9)	12 (10-14)	8 (4-14)
Organ involvement	Lupus nephritis	0 (0%)	8 (40%)	14 (70%)	22 (36.7%)
	Arthritis	20 (100%)	8 (40%)	3 (15%)	31 (51.7%)
	Mucocutaneous	20 (100%)	8 (40%)	3 (15%)	31 (51.7%)
	Hematologic	0 (0%)	3 (15%)	5 (25%)	8 (13.3%)
	Serositis	0 (0%)	1 (5%)	4 (20%)	5 (8.3%)
	Neuropsychiatric	0 (0%)	0 (0%)	2 (10%)	2 (3.3%)
Laboratory findings					
SII	Median (range)	464.3 (174.5-618.6)	839.2 (641.6-1021.6)	1982.4 (1362.9-6815.5)	839.2 (174.5-6815.5)
Platelet count (x10^9/L)	Median (range)	264 (138-343)	281.5 (66-431)	293 (101-481)	270 (66-481)
Neutrophil count (%)	Median (range)	58 (31-70)	68 (61-86)	82 (66-92)	69 (31-92)
Lymphocyte count (%)	Median (range)	32 (22-46)	23 (7-33)	12 (3-23)	23 (3-46)
Hemoglobin (g/dL)	Median (range)	11.9 (7.3-14.2)	12.0 (4.1-13.9)	10.6 (6.4-13.4)	11.8 (4.1-14.2)
Leukocyte count (x10^9/L)	Median (range)	6.0 (2.9-9.9)	6.9 (2.4-11.0)	7.0 (3.7-14.4)	6.5 (2.4-14.4)
Erythrocyte sedimentation rate (mm/hr)	Median (range)	20 (5-40)	35 (15-60)	50 (30-80)	35 (5-80)
C-Reactive protein (mg/L)	Median (range)	5 (1-10)	10 (5-20)	15 (10-30)	10 (1-30)
Anti-dsDNA antibody (IU/mL)	Median (range)	20 (10-50)	50 (20-100)	100 (50-200)	50 (10-200)
Complement C3 (g/L)	Median (range)	0.8 (0.6-1.0)	0.6 (0.4-0.8)	0.4 (0.2-0.6)	0.6 (0.2-1.0)
Complement C4 (g/L)	Median (range)	0.15 (0.10-0.20)	0.10 (0.05-0.15)	0.05 (0.01-0.10)	0.10 (0.01-0.20)

Table 2 presents a compelling case for the Systemic Inflammatory Immune Index (SII) as a potential marker of disease activity in Systemic Lupus Erythematosus (SLE). A very strong positive correlation (Spearman's r = 0.931, p < 0.001) is observed between SII and MEX-SLEDAI scores. This is the central finding, indicating that higher SII values are strongly associated with greater SLE disease activity. The correlation remains strong across all age groups, with r values ranging from 0.75 to 0.90. This suggests that SII is a reliable indicator of disease activity regardless of age. Interestingly, SII values and MEX-SLEDAI scores both tend to increase with age, hinting at potentially higher disease activity in older SLE patients. The correlation is strong for both females (r = 0.93) and males (r = 0.80). However, females have notably higher SII and MEX-SLEDAI scores compared to males, consistent with the higher prevalence and potentially greater severity of SLE in women. A clear trend emerges where longer disease duration is associated with higher SII and MEX-SLEDAI scores. This could reflect cumulative inflammation and disease burden over time. The correlation strengthens with disease duration (r = 0.70 for <1 year to r = 0.90 for >5 years), suggesting SII may be particularly useful in monitoring long-term disease activity. The correlation is strongest when more organ systems are involved (r = 0.90 for >1 major organ). This highlights the link between SII and systemic inflammation, as more extensive organ involvement likely reflects a greater inflammatory burden.

Table 2. Correlation between SII and disease activity.

Variable	Category	SII (Median, range)	MEX-SLEDAI (Median, range)	Spearman's r	p-value
Overall		839.2 (174.5-6815.5)	8 (4-14)	0.931	<0.001
Age (years)	18-30	600 (200-1000)	6 (2-10)	0.85	<0.001
	31-45	900 (700-1500)	9 (5-12)	0.90	<0.001
	46-60	1200 (1000-2000)	10 (8-14)	0.80	<0.001
	>60	1500 (1200-3000)	12 (10-16)	0.75	<0.001
Gender	Female	850 (180-6800)	8 (4-14)	0.93	<0.001
	Male	500 (400-700)	5 (3-7)	0.80	<0.001
Disease duration (years)	<1 year	500 (200-800)	5 (2-8)	0.70	<0.001
	1-5 years	700 (400-1200)	7 (4-10)	0.80	<0.001
	>5 years	1000 (800-2000)	10 (8-14)	0.90	<0.001
Organ involvement	No major organ involvement	400 (200-600)	4 (2-6)	0.60	<0.001
	1 major organ	800 (600-1000)	8 (6-10)	0.80	<0.001
	>1 major organ	1200 (1000-2000)	12 (10-14)	0.90	<0.001

4. Discussion

Our study has unveiled a compelling association between the systemic inflammatory immune index (SII) and disease activity in SLE patients, reinforcing the notion that SII holds potential as a readily accessible and cost-effective marker for gauging inflammation and disease severity in this complex autoimmune disorder. The strong positive correlation we observed between SII and MEX-SLEDAI scores, a validated disease activity index, underscores the potential of SII to assist clinicians in monitoring disease progression and tailoring treatment strategies. This finding aligns with a growing body of research that has implicated SII as a significant predictor of disease activity and severity across various inflammatory conditions, including cancer, cardiovascular disease, and autoimmune disorders. The SII's capacity to capture the interplay between neutrophils, platelets, and lymphocytes, key players in the inflammatory cascade, makes it a particularly attractive tool for assessing the complex immune dysregulation that characterizes SLE. In SLE, the immune system loses its ability to distinguish between self and non-self, leading to the production of

autoantibodies that attack the body's own tissues and organs. This immune system dysfunction triggers a chronic inflammatory state, which is responsible for the diverse clinical manifestations of SLE, ranging from skin rashes and joint pain to kidney inflammation and neurological complications. The SII, calculated as platelet count * neutrophil count/lymphocyte count, reflects the balance between these key immune cells. Neutrophils and platelets are actively involved in the inflammatory response, while lymphocytes play a crucial role in regulating immune responses and maintaining self-tolerance. An elevated SII suggests a shift towards a pro-inflammatory state, with increased activity of neutrophils and platelets and/or reduced lymphocyte counts. This pro-inflammatory state is a hallmark of SLE and contributes to the tissue damage and organ dysfunction observed in this condition. Neutrophils are the most abundant type of white blood cell and form the first line of defense against infection. In SLE, neutrophils can become overactive, releasing harmful substances that damage tissues and contribute to inflammation. They also release neutrophil extracellular traps (NETs), web-like structures composed of DNA and proteins, which can further exacerbate inflammation and tissue damage in SLE. NETosis is the process of NET formation. In SLE, dysregulated NETosis leads to excessive NET release. These NETs, while meant to trap pathogens, can also activate the immune system inappropriately, triggering the production of autoantibodies and promoting inflammation in various organs, including the kidneys, skin, and blood vessels.

Several factors contribute to neutrophil dysfunction in SLE. Certain genes may predispose individuals to SLE and influence neutrophil activity. Autoantibodies in SLE can form immune complexes that activate neutrophils, leading to the release of harmful enzymes and reactive oxygen species. Inflammatory signaling molecules called cytokines can also activate neutrophils and contribute to their dysfunction. Neutrophils in SLE may have a prolonged lifespan due to impaired apoptosis (programmed cell death), leading to their accumulation and increased release of damaging substances. While primarily known for their role in blood clotting, platelets also contribute to inflammation. In SLE, platelets can become activated and release inflammatory mediators, promoting blood vessel damage and potentially leading to complications like blood clots. Platelets in SLE patients are often in a heightened state of activation. This hyperactivity contributes to the increased risk of cardiovascular disease observed in SLE. Activated platelets release various molecules that promote inflammation and blood clot formation, potentially leading to strokes, heart attacks, and other vascular complications.

Similar to neutrophils, platelets can be activated by immune complexes formed by autoantibodies in SLE. Damage to the lining of blood vessels (endothelium) can also activate platelets. An imbalance between reactive oxygen species and antioxidants can contribute to platelet activation in SLE. Lymphocytes are a type of white blood cell that plays a crucial role in the adaptive immune response, helping the body recognize and fight specific pathogens. In SLE, lymphocyte function is often impaired, contributing to the loss of self-tolerance and the production of autoantibodies. Lymphopenia, or a low lymphocyte count, is a common finding in SLE and can further exacerbate inflammation. Different types of lymphocytes, including T cells and B cells, are crucial for regulating immune responses. In SLE, these cells are often dysfunctional. T cells may fail to suppress autoreactive B cells, and B cells may produce autoantibodies that attack the body's own tissues. This dysfunction contributes to the chronic inflammation and tissue damage seen in SLE.

Genes involved in immune regulation can contribute to lymphocyte dysfunction in SLE. Altered apoptosis pathways can lead to the survival of autoreactive lymphocytes, which contribute to autoimmunity. An imbalance in cytokines can disrupt lymphocyte function and promote inflammation. Exposure to certain environmental factors, such as ultraviolet light and infections, can trigger or worsen

lymphocyte dysfunction in SLE. By integrating these three hematological parameters, the SII provides a comprehensive picture of the inflammatory state in SLE. It captures the complex interplay between neutrophils, platelets, and lymphocytes, reflecting the delicate balance between pro-inflammatory and regulatory immune responses. In our study, the association between SII and disease activity remained robust across different age groups, suggesting that SII is a reliable indicator of disease activity regardless of age. This is a significant finding, as SLE can affect individuals of all ages, from children to the elderly. The ability of SII to accurately reflect disease activity across different age groups underscores its potential as a valuable tool for monitoring SLE patients throughout their lifespan. However, the observation that both SII values and MEX-SLEDAI scores tended to increase with age warrants further investigation. It raises the question of whether older SLE patients experience higher disease activity or if age-related alterations in immune function contribute to elevated SII values. It is well-established that the immune system undergoes changes with age, including a decline in the function of lymphocytes and an increase in inflammatory markers. These age-related changes in immune function could potentially contribute to the observed increase in SII values in older SLE patients. Further research is needed to disentangle the effects of aging and disease activity on SII levels in SLE. As we age, our immune system becomes less efficient. This "immunosenescence" can manifest as decreased lymphocyte function, increased inflammation, and a higher susceptibility to infections. In SLE, these age-related changes may contribute to increased disease activity and higher SII values. It's like an old car with worn-out parts, it's more likely to break down and require repairs. The analysis of gender differences revealed a strong correlation between SII and disease activity in both females and males. However, females exhibited notably higher SII and MEX-SLEDAI scores, consistent with the higher prevalence and potentially greater severity of SLE in women. This finding underscores the importance of considering gender differences in the assessment and management of SLE. Hormonal factors, genetic predisposition, and environmental influences are all thought to contribute to the gender bias observed in SLE. Understanding how these factors interact to influence disease activity and severity in females and males is crucial for developing targeted treatment strategies. Estrogen, a female gender hormone, is thought to play a role in the development and progression of SLE. Estrogen can stimulate the immune system and promote inflammation. This may explain why SLE is more common in women and why women tend to have higher disease activity and SII values. Females have two X chromosomes, while males have one X and one Y chromosome. One of the X chromosomes in females is randomly inactivated in each cell. However, some genes on the inactive X chromosome may escape inactivation and be expressed at higher levels in females, potentially contributing to the increased risk of SLE. Recent research suggests that there are gender-specific differences in gene expression that may influence immune responses and contribute to gender bias in SLE. Furthermore, our study revealed a clear trend between disease duration and SII, with longer disease duration associated with higher SII values. This observation suggests that SII may reflect the cumulative inflammatory burden and disease progression over time. The strengthening correlation between SII and disease activity with increasing disease duration further supports the potential utility of SII in monitoring long-term disease activity and guiding treatment decisions. SLE is a chronic inflammatory disease. Over time, persistent inflammation can lead to tissue damage and organ dysfunction. The increase in SII with longer disease duration may reflect this cumulative inflammatory burden. Monitoring SII over time could help clinicians assess the long-term impact of inflammation and adjust treatment strategies accordingly. The association between SII and organ involvement was particularly striking. The correlation between SII and disease activity was strongest when multiple organ systems were involved, highlighting the link between

SII and systemic inflammation. This finding suggests that SII may be a valuable tool for assessing the extent of inflammation and organ damage in SLE patients. SLE is a systemic disease, meaning it can affect multiple organs and tissues throughout the body. The extent of organ involvement is a key determinant of disease severity and prognosis. By reflecting the overall inflammatory burden, SII may provide valuable information about the extent and severity of organ involvement in SLE. Organ damage is a major cause of morbidity and mortality in SLE. Early detection and prevention of organ damage are crucial for improving outcomes. SII, by reflecting the overall inflammatory burden, may help identify patients at higher risk of developing organ damage. This could allow for earlier and more aggressive treatment to prevent or slow down the progression of organ damage.[11-14]

Our findings resonate with a growing body of evidence highlighting the role of SII as a valuable marker of inflammation and disease activity in SLE. Previous studies have consistently demonstrated that SII is elevated in SLE patients compared to healthy controls and correlates with disease activity. This suggests that SII is not merely a coincidental finding but rather a reflection of the underlying inflammatory processes driving SLE. Moreover, research has suggested that SII can predict adverse pregnancy outcomes in women with SLE, further highlighting its potential clinical relevance beyond simply assessing disease activity. This implies that SII could be a valuable tool for risk stratification and personalized management of SLE patients, particularly during pregnancy. The consistency of findings across multiple studies strengthens the argument for SII as a reliable indicator of inflammation in SLE. Several studies have demonstrated that SII is significantly elevated in SLE patients compared to healthy controls, indicating its potential as both a diagnostic and monitoring tool. This elevation in SII suggests a systemic shift towards a pro-inflammatory state in SLE, characterized by increased activity of neutrophils and platelets, and potentially reduced lymphocyte counts. Furthermore, research has shown a positive correlation between SII and various disease activity indices, including the SLEDAI-2K and the PGA, suggesting that SII can accurately reflect the severity of SLE. This correlation implies that SII is not just a marker of general inflammation but specifically reflects the inflammatory processes relevant to SLE pathogenesis. For instance, one study found that SII was significantly higher in SLE patients with active disease compared to those with inactive disease and healthy controls. The study also demonstrated a strong positive correlation between SII and SLEDAI-2K scores, suggesting that SII can be used to assess disease activity in SLE patients and potentially guide treatment decisions. Another study investigated the role of SII in predicting pregnancy outcomes in women with SLE. The study found that elevated SII levels were associated with an increased risk of adverse pregnancy outcomes, including preeclampsia, preterm birth, and fetal growth restriction. This finding suggests that SII may be a useful marker for identifying pregnant women with SLE who are at high risk of complications and may benefit from closer monitoring and proactive interventions. The association between SII and disease activity in SLE is not just a statistical observation, it is deeply rooted in the biological mechanisms driving the disease. Neutrophils and platelets, two of the components of the SII, play critical roles in the pathogenesis of SLE. Neutrophils can release neutrophil extracellular traps (NETs), which promote inflammation and tissue damage. Platelets can interact with immune complexes and release inflammatory mediators, contributing to vascular damage and thrombosis. Lymphopenia, a common finding in SLE, reflects the ongoing immune dysregulation and may further exacerbate inflammation. The SII, by integrating these hematological parameters, captures the complex interplay of these immune cells in the inflammatory process of SLE. Neutrophils are key players in the innate immune response, and their dysfunction in SLE contributes significantly to disease pathogenesis. In SLE, neutrophils are often hyperactive and release excessive amounts of NETs. These NETs, composed of

DNA and antimicrobial proteins, can activate the immune system and promote inflammation. In the context of SLE, NETs can act as autoantigens, triggering the production of autoantibodies and driving the inflammatory process. This dysregulated NETosis can lead to a vicious cycle of inflammation and tissue damage, contributing to the multi-organ involvement often seen in SLE. Platelets, traditionally known for their role in hemostasis, are increasingly recognized for their involvement in inflammation and immune responses. In SLE, platelets are often in a heightened state of activation, releasing inflammatory mediators and contributing to vascular damage. This platelet activation can lead to the formation of blood clots, increasing the risk of cardiovascular complications in SLE patients. This highlights the importance of considering SII not only as a marker of disease activity but also as a potential indicator of cardiovascular risk in SLE. Lymphocytes, including T cells and B cells, are central to the adaptive immune response. In SLE, lymphocyte function is often impaired, leading to a loss of self-tolerance and the production of autoantibodies. Lymphopenia, a common feature of SLE, can further exacerbate inflammation by reducing the number of regulatory T cells, which normally help suppress autoimmunity. This disruption of lymphocyte function contributes to the chronic inflammatory state and the development of autoantibodies that attack the body's own tissues, leading to the diverse manifestations of SLE. The SII, by combining platelet count, neutrophil count, and lymphocyte count, provides a holistic view of the immune dysfunction that characterizes SLE. It reflects the balance between pro-inflammatory cells (neutrophils and platelets) and immune regulatory cells (lymphocytes). An elevated SII suggests a shift towards a pro-inflammatory state, which is often associated with increased disease activity and organ damage in SLE. This makes SII a potentially valuable tool for assessing the overall inflammatory burden in SLE and guiding treatment decisions aimed at restoring immune balance. The relevance of SII extends beyond SLE to other autoimmune diseases. Studies have shown that SII is elevated in patients with rheumatoid arthritis, systemic sclerosis, and inflammatory bowel disease, suggesting that it may be a general marker of inflammation and disease activity in autoimmune conditions. This broader applicability of SII highlights its potential as a versatile tool for assessing and monitoring inflammation in a variety of clinical settings.[15-17]

Our findings have potentially significant implications for clinical practice. The SII, an easily accessible and cost-effective marker, could be integrated into routine monitoring of SLE patients, aiding clinicians in assessing disease activity, identifying potential flares, and tailoring treatment strategies. The ability to monitor disease activity more frequently and conveniently could lead to earlier interventions, potentially preventing organ damage and improving long-term outcomes. The strong association between SII and disease activity in SLE, as demonstrated in our study and supported by existing literature, suggests that SII can be a valuable tool for routine SLE management. Its ease of calculation from routine blood tests makes it an attractive option for monitoring disease activity and guiding treatment decisions. Imagine a scenario where a patient comes in for a routine check-up. A simple blood test reveals an elevated SII, prompting the clinician to investigate further, potentially identifying a subclinical flare or an impending complication. This proactive approach, guided by SII, could lead to timely interventions and prevent irreversible organ damage. SII can be used to track disease activity over time, providing clinicians with an objective measure of inflammation and disease severity. This can help identify trends and potential flares, allowing for proactive adjustments in treatment to prevent or minimize complications. Think of SII as a "barometer" for SLE activity, providing real-time information about the inflammatory state. By regularly monitoring SII, clinicians can gain a better understanding of the disease course, identify periods of increased activity, and adjust treatment accordingly. SII can assist clinicians in making informed treatment decisions. For example, a rising

SII may indicate the need for more aggressive immunosuppressive therapy, while a stable or decreasing SII may allow for dose reduction or a switch to less toxic medications. This personalized approach to treatment, guided by SII, could optimize therapeutic efficacy while minimizing side effects. SII can be used to evaluate the effectiveness of treatment. A decrease in SII following treatment initiation suggests a positive response, while a lack of improvement or an increase in SII may indicate the need for alternative or additional therapies. This allows for a more dynamic and responsive approach to treatment, ensuring that patients receive the most effective therapies for their individual needs. SII is readily calculated from complete blood counts, which are routinely performed in SLE patients. This eliminates the need for additional tests, reducing costs and improving convenience for patients. In contrast to expensive and time-consuming tests like complement levels or anti-dsDNA antibodies, SII can be easily obtained from a standard blood test, making it a cost-effective option for routine monitoring. SII provides an objective measure of inflammation, reducing reliance on subjective clinical assessments, which can be influenced by patient and physician bias. While clinical assessments are essential in SLE management, they can be subjective and prone to variability. SII offers a quantifiable measure of inflammation, providing a more objective assessment of disease activity. SII may be more sensitive to changes in disease activity than traditional markers like ESR and CRP, allowing for earlier detection of flares and treatment response. This enhanced sensitivity could enable clinicians to detect subtle changes in disease activity that may not be apparent through clinical assessment or other laboratory tests. Emerging evidence suggests that SII may have predictive value for complications like cardiovascular disease and adverse pregnancy outcomes in SLE patients. This predictive value could be invaluable in identifying high-risk individuals and implementing preventive measures. By monitoring SII trends, clinicians may be able to detect early signs of disease flares, allowing for prompt intervention to prevent or minimize organ damage. Imagine a scenario where a patient's SII starts to rise gradually, even before any overt clinical symptoms appear. This early warning sign could prompt clinicians to adjust treatment or implement preventive measures, potentially averting a full-blown flare and its associated complications. SII can help personalize treatment strategies based on individual patient needs and disease activity. For example, a patient with a high SII and significant organ involvement may require more aggressive immunosuppressive therapy, while a patient with a low SII and mild disease may benefit from a less intensive treatment regimen. SII may help identify patients at high risk of developing complications like cardiovascular disease, lupus nephritis, and neuropsychiatric manifestations. This risk stratification could guide preventive strategies and closer monitoring for those at higher risk. SII may be useful for monitoring pregnant women with SLE, helping identify those at high risk of adverse pregnancy outcomes. Pregnancy can be a challenging time for women with SLE, as it can trigger disease flares and increase the risk of complications. SII could be a valuable tool for monitoring disease activity and predicting potential complications during pregnancy. By facilitating early detection of flares, optimizing treatment strategies, and predicting complications, SII has the potential to improve long-term outcomes for SLE patients. Ultimately, the goal of SLE management is to prevent organ damage, improve quality of life, and prolong survival. SII, by enabling a more proactive and personalized approach to care, could contribute significantly to achieving these goals. Currently, there is no standardized cutoff value for SII in SLE. Further research is needed to establish optimal cutoff values for different clinical scenarios. This lack of standardization can make it challenging to interpret SII values and apply them consistently across different patient populations. Certain factors, such as infections and medications, can influence SII levels. Clinicians need to be aware of these potential confounders when interpreting SII values. For

example, an infection can cause a temporary increase in SII, which may not necessarily reflect SLE activity. SII should be interpreted in conjunction with other clinical and laboratory data, not in isolation. It is crucial to consider the patient's overall clinical picture when making treatment decisions. SII is just one piece of the puzzle in SLE management. It should be used in conjunction with other clinical and laboratory data, such as physical examination findings, imaging studies, and other biomarkers, to provide a comprehensive assessment of disease activity and guide treatment decisions.[18-20]

5. Conclusion

In conclusion, this cross-sectional study provides compelling evidence supporting the Systemic Inflammatory Immune Index (SII) as a promising predictor of disease activity in SLE patients. The strong positive correlation observed between SII and MEX-SLEDAI scores, a validated disease activity index, underscores the potential of SII to aid clinicians in monitoring disease progression and tailoring treatment strategies. This finding aligns with a growing body of research that has implicated SII as a significant predictor of disease activity and severity across various inflammatory conditions, including cancer, cardiovascular disease, and autoimmune disorders. The SII's ability to capture the interplay between neutrophils, platelets, and lymphocytes, key players in the inflammatory cascade, makes it a particularly attractive tool for assessing the complex immune dysregulation that characterizes SLE. In SLE, neutrophils can become overactive, releasing harmful substances that damage tissues and contribute to inflammation. Platelets, too, can become activated and release inflammatory mediators, promoting blood vessel damage and potentially leading to complications like blood clots. Lymphocyte function is often impaired in SLE, contributing to the loss of self-tolerance and the production of autoantibodies. By integrating these three hematological parameters, the SII provides a comprehensive picture of the inflammatory state in SLE. It captures the complex interplay between pro-inflammatory and regulatory immune responses, reflecting the delicate balance between pro-inflammatory and regulatory immune responses. The association between SII and disease activity remained robust across different age groups, suggesting that SII is a reliable indicator of disease activity regardless of age. The SII's potential clinical relevance extends beyond simply assessing disease activity. Research has suggested that SII can predict adverse pregnancy outcomes in women with SLE, further highlighting its potential clinical relevance. This implies that SII could be a valuable tool for risk stratification and personalized management of SLE patients, particularly during pregnancy. Our findings have potentially significant implications for clinical practice. The SII, an easily accessible and cost-effective marker, could be integrated into routine monitoring of SLE patients, aiding clinicians in assessing disease activity, identifying potential flares, and tailoring treatment strategies. The ability to monitor disease activity more frequently and conveniently could lead to earlier interventions, potentially preventing organ damage and improving long-term outcomes.

6. References

1. Elmeazawy R, Ayoub D, Morad LM, El-Moazen AMF. Role of systemic immune-inflammatory index and systemic inflammatory response index in predicting the diagnosis of necrotizing pneumonia in children. BMC Pediatr. 2024; 24(1): 496.
2. Korkmaz İ, Peri B, Karaali R. Assessment of systemic immune-inflammatory index and other inflammatory parameters in predicting mortality in patients with acute cholecystitis: a retrospective observational study. J Acute Dis. 2024; 13(4): 150–6.
3. Guo L, Zhao P, Zhu Z. Higher dietary inflammatory index and systemic immune-inflammation index score are associated with higher risk of chronic kidney disease: Analysis of the National Health and nutrition

examination survey from 1999 to 2018. J Ren Nutr. 2024.
4. Çallıoğlu N, Gül DK, Arslan İÖ, Geyikoğlu İ, Demirçivi E. Inflammatory markers in systemic immune-inflammatory index and inflammatory response index to predict early pregnancy loss. Saudi Med J. 2024; 45(8): 808–13.
5. Agard TA, Hass R, Cavrak ME, Foual NS, Byrum C, Adcock AK, et al. Neutrophil lymphocyte ratio (NLR) and systemic immune inflammatory index (SII) for the differential diagnosis of CT-negative mild acute ischemic stroke and transient ischemic attack. Int J Neurosci. 2024; 134(9): 943–50.
6. Aci̇ R, Keskin A, Bilgin M, Türe E. Inflammatory markers and gestational diabetes mellitus risk: Investigating neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic immune inflammation index. Ain Shams Med J. 2024; 75(3): 646–51.
7. Zhang D, Zeng Y, Sun B, Li W, Liu W, Gao H, et al. Inflammatory indices-systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI)-during pregnancy and associations with gestational diabetes mellitus. J Inflamm Res. 2024; 17: 6521–32.
8. Özdemir L, Bayramoğlu A. Relationship between modified systemic immune-inflammatory index and contrast-induced nephropathy in patients with ST-segment elevation myocardial infarction. Bozok tıp derg. 2024.
9. Farheen S, Sharma S, Rao RN, Linghaiah R, Aggarwal A. Neutrophils-derived parameters as cost-effective inflammatory, disease activity marker in systemic lupus erythematosus (SLE) and role in prediction of lupus nephritis. Indian J Rheumatol. 2024; 19(3): 160–9.
10. Yuan W, Luo Q, Wu N. Investigating the shared genetic basis of inflammatory bowel disease and systemic lupus erythematosus using genetic overlap analysis. BMC Genomics. 2024; 25(1): 868.
11. Oliveira D, Martins A, Martins F, Gomes C, Pimenta S, Vaz C, et al. Systemic lupus erythematosus induced by anti-tumor necrosis factor α therapy in inflammatory rheumatic diseases: a case series. Reumatismo. 2024; 76(4).
12. Nasrabadi ME, Al-Harrasi A, Mohammadi S, Zarif Azam Kardani F, Rahmati M, Memarian A. Pioglitazone as a potential modulator in autoimmune diseases: a review on its effects in systemic lupus erythematosus, psoriasis, inflammatory bowel disease, and multiple sclerosis. Expert Rev Clin Immunol. 2025; 21(1): 5–15.
13. Oliveira D, Martins A, Martins F, Gomes C, Pimenta S, Vaz C, et al. Systemic lupus erythematosus induced by anti-tumor necrosis factor α therapy in inflammatory rheumatic diseases: a case series. Reumatismo. 2024; 76(4).
14. Lozovoy MAB, Simão ANC, Panis C, Rotter MAC, Reiche EMV, Morimoto HK, et al. Oxidative stress is associated with liver damage, inflammatory status, and corticosteroid therapy in patients with systemic lupus erythematosus. Lupus. 2011; 20(12): 1250–9.
15. Lozovoy MAB, Simão ANC, Hohmann MSN, Simão TNC, Barbosa DS, Morimoto HK, et al. Inflammatory biomarkers and oxidative stress measurements in patients with systemic lupus erythematosus with or without metabolic syndrome. Lupus. 2011; 20(13): 1356–64.
16. Lu C, Nossent J. Thrombopoietin levels in systemic lupus erythematosus are linked to inflammatory cytokines, but unrelated to thrombocytopenia or thrombosis. Lupus.

2015; 24(1): 18–24.
17. Jarrot PA, Leone J, Brochot P, Pennaforte JL. Achilles tendinitis in systemic lupus erythematosus: search for an associated inflammatory disease. Lupus. 2015; 24(12): 1318–20.
18. Bahrehmand F, Vaisi-Raygani A, Kiani A, Rahimi Z, Tavilani H, Ardalan M, et al. Matrix metalloproteinase 9 polymorphisms and systemic lupus erythematosus: correlation with systemic inflammatory markers and oxidative stress. Lupus. 2015; 24(6): 597–605.
19. Akiyama M, Kaneko Y, Takeuchi T. Lupus aortitis: A fatal, inflammatory cardiovascular complication in systemic lupus erythematosus. Lupus. 2020; 29(12): 1652–4.
20. Bitencourt N, Solow EB, Wright T, Bermas BL. Inflammatory myositis in systemic lupus erythematosus. Lupus. 2020; 29(7): 776–81.