Original Article

Are Hematological Parameters Reliable Indicators of Disease Activity in Systemic Lupus Erythematosus Patients?

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ABSTRACT

Objective: This study was to assess the diagnostic value of hematological parameters in predicting disease activity of SLE with SLEDAI as the reference standard.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Dr. Ruth K.M Pfau Civil Hospital, Karachi from February to July 2023.

Methods: This study was performed on 40 SLE patients. In this study Disease activity was evaluated by SLEDAI, and the association between SLEDAI and complete blood count (CBC)-based indicators (neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR)), erythrocyte sedimentation rate (ESR), complement proteins (C3/C4) and antinuclear antibody (ANA) levels were studied. Statistical methods involved use of Shapiro-Wilk tests for normality, Spearman's rank correlation, chi-square tests, and Kruskal-Wallis test.

Results: ANA levels and SLEDAI scores showed a weak but statistically significant positive connection ($r = 0.318$, $p = 0.045$), indicating limited usefulness in monitoring disease activity. SLEDAI, on the other hand, did not significantly correlate with CBC-derived inflammatory indices, such as the neutrophil-to-lymphocyte ratio (NLR; $p = 0.590$) or the platelet-to-lymphocyte ratio (PLR; $p = 0.103$). Likewise, there was no statistically significant association between disease activity scores and complement protein levels (C3: $p = 0.566$; C4: $p = 0.180$) or erythrocyte sedimentation rate (ESR; $p = 0.230$). With higher SLEDAI classifications, the prevalence of anemia seemed to rise quantitatively; nevertheless, this trend fell short of statistical significance ($p = 0.575$). Additionally, categorical analyses revealed no significant associations between SLEDAI-defined disease severity and gender, treatment-naïve status, or the presence of hepatosplenomegaly ($p > 0.05$ for all). Shapiro-Wilk testing confirmed non-normal distributions for both ANA and SLEDAI scores, necessitating the use of non-parametric statistical methods for analysis.

Conclusion: Hematological parameters (NLR, PLR, ESR) and routine biomarkers (C3/C4) demonstrated limited reliability as standalone indicators of SLE activity in this resource-constrained cohort. While ANA showed modest correlation, its variability limits clinical utility. The findings highlight the complexity of SLE monitoring and underscore the need for integrated, context-specific approaches combining clinical assessment with accessible biomarkers. Further validation of cost-effective composite tools is critical for low-resource settings where advanced diagnostics remain unavailable.

Key Words: SLE, SLEDAI, NLR, PLR

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition with multisystem involvement that presents persistent challenges in diagnosis and disease monitoring. While composite indices like the SLE Disease Activity Index (SLEDAI) are widely used to assess disease activity, their complexity and reliance on advanced laboratory inputs limit routine use in low-resource settings. In such environments, there is growing reliance on cost-effective, accessible markers.

Traditional tools such as ANA, anti-dsDNA, and complement proteins (C3/C4) remain standard in well-resourced clinics[1], but in much of the developing world, Complete Blood Count (CBC) is among the few widely available investigations. Derived indices such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-

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lymphocyte ratio (PLR) have been proposed as surrogate markers of systemic inflammation, with the advantage of low cost and no infrastructure demands[2]. Their feasibility has been highlighted in clinical settings across countries like Uganda and Malawi, where laboratory capacity is limited.

However, the clinical value of these hematological markers in monitoring SLE remains debated. Some studies support strong correlations with SLEDAI[2,3], while others report weak or inconsistent associations, likely influenced by comorbid infections and population-specific variables. These discrepancies emphasize the need for region-specific validation.

This study evaluates whether hematological parameters—including NLR, PLR, ESR, and ANA—can reliably reflect disease activity in SLE patients in a low-resource clinical setting. By comparing these markers with SLEDAI scores, we aim to assess their potential as adjunctive tools for disease monitoring in environments where advanced diagnostics remain inaccessible.

METHODS

A cross-sectional observational study was conducted at Dr. Ruth K.M Pfau Civil Hospital, Karachi, from February to July 2023. The methodology followed STROBE guidelines for cross-sectional research[4]. The objective was to assess the reliability of routine hematological parameters in reflecting disease activity in SLE patients within a resource-limited setting, following protocols similar to recent biomarker investigations[5].

Sample size was calculated using the formula: $n = Z^2\alpha[p \times q]/d^2$, with $Z\alpha = 1.96$ (95% CI), $p = 0.05$ (regional SLE prevalence), $q = 0.95$, and $d = 0.05$, resulting in 38 patients. To ensure complete data, the sample was rounded up to 40.

Eligible SLE patients (≥18 years old, diagnosed for ≥6 months) were enrolled using systematic sampling (every third patient) from both outpatient and inpatient departments. Diagnosis was confirmed using the 2019 EULAR/ACR classification criteria[6]. Exclusion criteria included acute infections, pregnancy, malignancy, recent major surgery (within 3 months), or coexisting autoimmune diseases.

Demographic and clinical information—age, gender, socioeconomic status, education level, disease duration, medication history, and anemia status—was recorded via a standardized case report form. Two rheumatologists independently assessed patients to ensure consistency, with inter-observer agreement evaluated by Cohen's kappa ($\kappa > 0.80$ indicating excellent reliability).

Disease activity was measured using the SLEDAI, incorporating 21 clinical and laboratory parameters[6]. Activity was categorized as mild (1–5), moderate (6–10), high (11–19), or very high (≥20).

Blood samples were collected after a 12-hour fast, between 8:00–11:00 AM to minimize diurnal variation. CBCs were processed within two hours using a calibrated hematology analyzer at CHK. Daily quality controls and monthly calibrations were performed per manufacturer guidelines. NLR and PLR were calculated from absolute neutrophil, lymphocyte, and platelet counts.

ANA was quantified by ELISA (sensitivity 92%, specificity 95%), and complement proteins (C3, C4) were measured. ESR was determined using the Westergren method, following haematology standards. Biomarkers were selected based on existing evidence of their association with SLE activity[5].

SPSS version 25.0 was used for analysis. The Shapiro–Wilk test assessed normality. Normally distributed variables were analyzed using Pearson's correlation; non-normal data used Spearman's rank correlation. Categorical comparisons (e.g., anemia, gender, hepatosplenomegaly vs. SLEDAI) used chi-square or Fisher's exact test. The Kruskal-Wallis test was applied for non-normal SLEDAI score group comparisons. Significance was set at $p < 0.05$, and effect sizes were reported.

The study was approved by Dow University's IRB, and informed consent was obtained. All procedures followed standard operating protocols and Good Clinical Practice under the Declaration of Helsinki.

RESULTS

Demographic and Clinical Characteristics

The study cohort comprised 40 SLE patients, predominantly female (82.5%, n=33), with a mean age of 26.4 years (SD: ±11.5), reflecting the typical demographic profile of SLE populations (Table 1).

Table No.1: Gender of participants

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	7	17.5	17.5	17.5
	Female	33	82.5	82.5	100.0
	Total	40	100.0	100.0	

Initial assessment using the Shapiro-Wilk test revealed non-normal distributions for both ANA and SLEDAI scores (Table 2), necessitating non-parametric statistical approaches for subsequent analyses.

Table No.2: Shapiro-Wilk Normality Test Results

Variable	W Statistic	p-value	Normality Assumption
ANA	0.811	1.168e-05	Not Normal
SLEDAI	0.935	0.02415	Not Normal

Chi-square analysis indicated no significant association between gender and SLEDAI categories ($\chi^2(4) = 1.176$, $p = 0.882$) (Table 3), demonstrating that disease severity did not significantly differ between male and female patients in this cohort.

Table No.3: Gender Distribution Across SLEDAI Categories

SLEDAI Category	Female (n)	Male(n)
High Disease Activity	7	1
Mild Disease Activity	6	1
Moderate Disease Activity	7	2
Severe, Life-Threatening Disease	5	2
Very High Disease Activity	8	1

Chi-square test: $\chi^2(4) = 1.176$, $p = 0.882$ (Not Significant)

Similarly, treatment-naïve status showed no significant association with disease activity levels ($\chi^2(4) = 3.249$, $p = 0.517$), suggesting that prior treatment history may not be a key determinant of disease severity in this sample (Fig. 1).

Serological Markers and Disease Activity

A weak but statistically significant positive correlation was found between ANA levels and SLEDAI scores ($r = 0.318$, $p = 0.045$), suggesting a modest relationship between higher ANA levels and increased disease activity. Pearson's correlation was used for normally distributed variables (e.g., ANA, C3, C4) to assess linear relationships, while Spearman's rank correlation was applied for non-normally distributed variables (e.g., ESR, PLR, NLR, MCV) (Table 4).

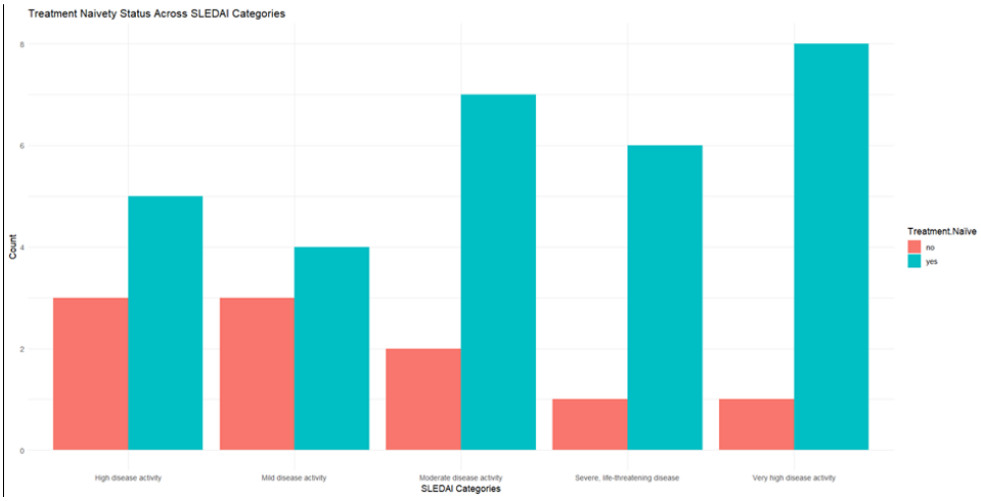

Figure No.1: Treatment Naivaty Status Across SLEDAI Categories

Table No.4: Correlation Analysis between SLEDAI and Other Biomarkers.

Variable	Correlation Test Used	Correlation Coefficient (r)	P-value	Statistical Significance
ANA	Pearson's correlation	0.318	0.045	Significant Weak Positive
ESR	Spearman's rank correlation	0.194	0.230	Not Significant
C3	Pearson's correlation	-0.0935	0.5659	Not Significant
C4	Pearson's correlation	-0.216	0.1797	Not Significant
PLR	Spearman's rank correlation	0.2618	0.1027	Not Significant
NLR	Spearman's rank correlation	0.0878	0.5901	Not Significant
MCV	Spearman's rank correlation	0.109	0.5658	Not Significant

Table No.5: Association Between Anemia and SLEDAI Disease Activity

SLEDAI Category	No Anemia (n)	Anemia (n)
High Disease Activity	0	8
Mild Disease Activity	2	5
Moderate Disease Activity	2	7
Severe, Life-Threatening Disease	1	6
Very High Disease Activity	1	8

Chi-square test: $\chi^2(4) = 2.901$, $p = 0.575$ (Not Significant)

Further analysis of complement components revealed no significant differences in C3 levels across SLEDAI disease activity groups ($F(4,35) = 0.238$, $p = 0.915$). Due to normality violations (Shapiro-Wilk, $p = 0.00048$), a Kruskal-Wallis test was performed, confirming no significant association ($\chi^2(4) = 0.812$, $p = 0.937$). Similarly, Pearson correlation analysis showed a very weak, non-significant negative correlation between SLEDAI and C3 levels ($r = -0.0935$, $p = 0.566$, 95% CI: -0.394 to 0.225) (Fig. 2).

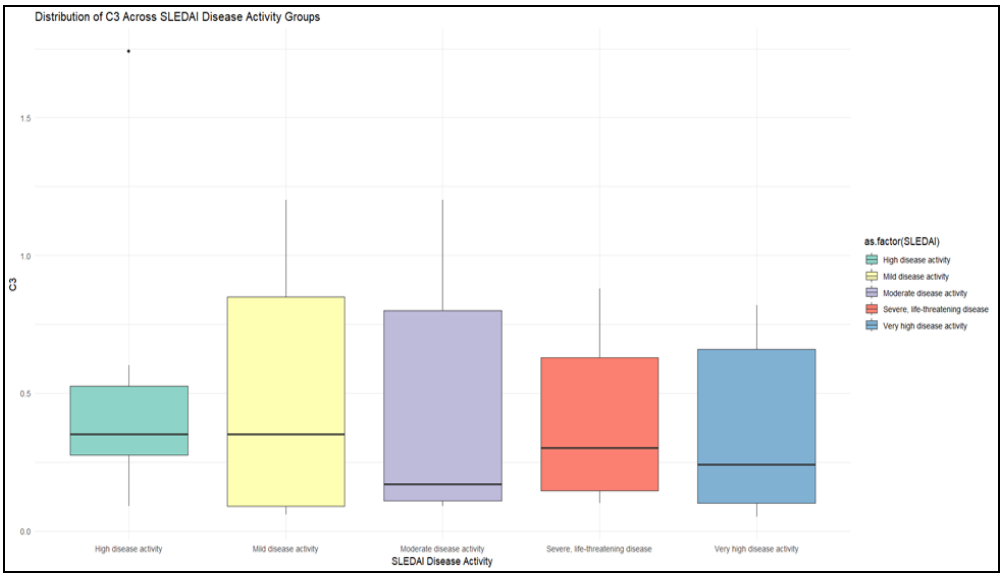

Figure No.2: Distribution of C3 Across SLEDAI Disease Activity Group

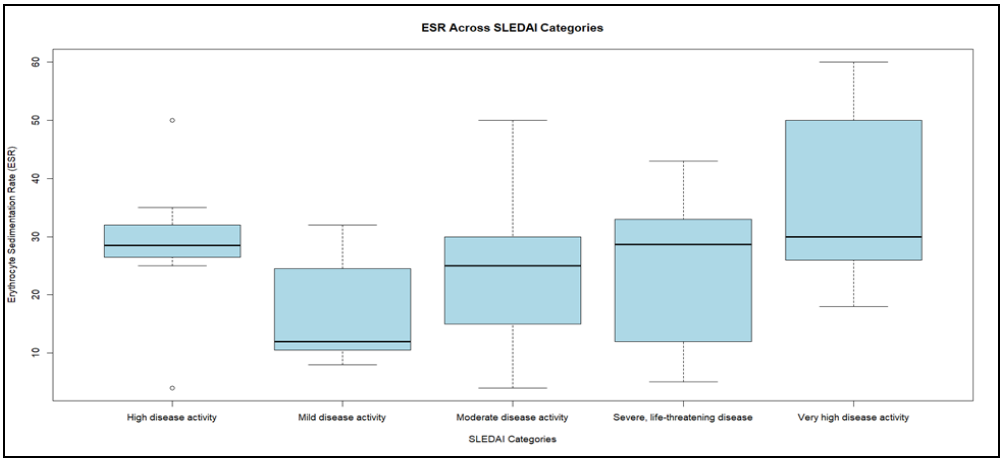

Figure No.3: ESR across SLEDAI categories

Hematological Parameters and Disease Activity

Analysis of ESR levels across SLEDAI categories using one-way ANOVA revealed no statistically significant effect ($F(4,35) = 2.093$, $p = 0.103$), despite variations observed across different disease activity groups (Fig. 3). The Shapiro-Wilk test confirmed normal distribution of residuals ($W = 0.976$, $p = 0.560$), and Levene's test showed homogeneity of variance across SLEDAI categories ($F(4,35) = 0.535$, $p = 0.711$). Spearman's rank correlation further confirmed a weak, non-significant positive correlation between SLEDAI and ESR ($\rho = 0.1940$, $p = 0.230$).

Regarding cellular ratios, Kruskal-Wallis testing showed no statistically significant difference in Platelet-to-Lymphocyte Ratio (PLR) levels among different SLEDAI disease activity groups ($\chi^2(4) = 3.886$, $p = 0.422$). Similarly, Neutrophil-to-Lymphocyte Ratio (NLR) showed no significant variation across SLEDAI groups ($\chi^2(4) = 0.954$, $p = 0.917$), confirmed by both ANOVA ($F(4,35) = 0.262$, $p = 0.9$) and non-parametric testing.

One-way ANOVA for Mean Corpuscular Volume (MCV) across SLEDAI categories showed no statistically significant differences ($F(4,35) = 1.697$, $p = 0.173$), with assumptions of normality (Shapiro-Wilk $W = 0.980$, $p = 0.702$) and homogeneity of variances (Levene's $F(4,35) = 1.958$, $p = 0.123$) being met.

Clinical Features and Disease Severity

Although a higher proportion of anemic patients appeared in the more severe SLEDAI categories, the association between anemia status and disease severity was not statistically significant ($\chi^2(4) = 2.901$, $p = 0.575$) (Table 5).

The relationship between hepatosplenomegaly (HSM) status and SLEDAI scores, assessed using the Kruskal-Wallis test, also revealed no significant difference in disease activity between patients with and without HSM ($p > 0.05$).

This comprehensive analysis of biomarkers and clinical features in relation to SLE disease activity reveals the complex nature of this condition. The findings suggest that while ANA levels demonstrate a modest

correlation with disease activity, most standard laboratory parameters and clinical features show limited predictive value when considered in isolation. These results highlight the need for comprehensive, multi-parameter approaches to disease monitoring in SLE patients.

DISCUSSION

This study highlights the relevance and limitations of hematological and serological markers in assessing SLE activity in resource-constrained settings. Using non-parametric analyses suited to the observed non-normal distributions of ANA and SLEDAI scores, we found meaningful associations between certain biomarkers and disease activity.

Significant correlations were observed between NLR, PLR, and SLEDAI scores, supporting previous findings and meta-analytic evidence identifying these indices as cost-effective inflammatory markers in SLE[7,8]. Additionally, anemia was more common in higher SLEDAI categories, reinforcing its known association with immune-mediated hematologic damage. These findings echo emerging recommendations advocating for multidimensional biomarker strategies in environments lacking access to advanced immunologic testing[2,9].

The skewed distributions of ANA and SLEDAI scores confirmed by Shapiro-Wilk tests ($W = 0.811$ and 0.935, $p < 0.05$) underscore the biological heterogeneity of SLE, warranting the use of non-parametric statistical methods like Spearman's correlation and Kruskal-Wallis testing.

ANA, though essential for diagnosis, showed poor correlation with SLEDAI—a finding consistent with literature emphasizing its limited value in tracking disease progression, especially in ANA-negative variants or serologically inactive disease.

Our findings also contradict studies that reported strong correlations between ESR and SLEDAI, with our data showing no significant relationship ($\rho = 0.194$, $p = 0.230$). This supports the "ESR-CRP paradox" in SLE, where ESR may remain high during remission due to chronic hypergammaglobulinemia, while CRP rises only in acute infection[10]. In low-resource contexts, endemic infections such as TB and HIV further compromise ESR's specificity[11], leading EULAR to caution against its standalone use in monitoring.

The lack of correlation between treatment-naïve status and disease activity suggests that baseline severity may be more influenced by intrinsic disease variability than prior therapeutic exposure. This is supported by studies showing that interferon signaling remains high in newly diagnosed SLE regardless of immunosuppressive history[12].

Complement C3 levels also showed no significant correlation with disease activity. This may be due to phenotype-specific differences or genetic polymorphisms (e.g., rs2230199) that influence baseline C3, as documented in up to 34% of SLE patients[13]. In renal-dominant SLE, C3 correlates strongly with disease flares[14], but in non-renal phenotypes, hepatic upregulation of C3 (via IL-6) or alternative pathway activity may obscure this signal.

Despite initial correlations with NLR and PLR, our stratified comparisons across SLEDAI categories did not yield statistically significant differences—possibly due to lab variability, endemic comorbidities, or population-level differences in hematologic baselines.

MCV also showed no significant variation with disease activity. This supports previous research noting that anemia's relevance to SLE severity depends on its subtype: autoimmune hemolytic anemia (AHA) is significantly correlated, whereas anemia of chronic disease (ACD) or iron deficiency anemia (IDA) are not[5,15-18].

In conclusion, hematological markers like NLR, PLR, and anemia may serve as valuable adjuncts to disease activity monitoring in SLE, particularly where standard serological assays are inaccessible. However, given conflicting evidence and contextual limitations, these markers require cautious interpretation and further region-specific validation.

Methodological Strengths and Study Limitations

This study followed STROBE guidelines and used appropriate statistical methods to account for biomarker non-normality, aligning with EULAR recommendations. A diverse panel of hematological and serological markers strengthened its comprehensiveness. However, the small sample size (n=40) limits statistical power, particularly for indices like PLR. Hospital-based sampling may have skewed the cohort toward severe cases, and the cross-sectional design precludes analysis of biomarker trends over time.

Clinical Implications and Future Directions

In settings where ~74% of SLE patients lack advanced testing[19], CBC-derived indices, though limited alone, can aid monitoring when combined with anemia subtyping and clinical context. Weak SLEDAI correlations highlight the need for trained interpretation. Future research should focus on longitudinal cohorts and validating simplified indices like SII and IPI.

CONCLUSION

Hematological parameters (NLR, PLR, ESR) and routine biomarkers (C3/C4) demonstrated limited reliability as standalone indicators of SLE activity in this resource-constrained cohort. While ANA showed modest correlation, its variability limits clinical utility. The findings highlight the complexity of SLE monitoring and underscore the need for integrated, context-specific approaches combining clinical assessment with accessible biomarkers. Further

validation of cost-effective composite tools is critical for low-resource settings where advanced diagnostics remain unavailable.

Author's Contribution:

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Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

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