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UTILITY OF RED CELL DISTRIBUTION WIDTH (RDW) IN ASSESSING DISEASE SEVERITY AND FLARES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder1 characterised by periods of inactivity and remission that can result in significant morbidity if overlooked. Classical DAIs including the systemic lupus erythematosus disease activity index (SLEDAI), complement levels and anti-dsDNA antibody titers are expensive, time consuming and often not available in low resource settings. Here, we assess whether the Red Cell Distribution Width (RDW) as a routine hematologic parameter could be helpful to serve as a biomarker for the evaluation of disease activity and prediction of flares in SLE. A cross-sectional analytical study was carried out in the rheumatology department, Tertiary Care Hospital, Karachi for a period of 12 months in 2024. One hundred twenty (n = 120) SLE cases meeting EULAR/ACR 2019 classification criteria were included by consecutive sampling. Demographic and clinical characteristics, as well as laboratory results (including the RDW, ESR, CRP; complement (C3 and C4) levels; anti-dsDNA), were collected. Disease activity was assessed according to the SLEDAI-2K score. Statistical methods included Pearson correlation, ANOVA, Receiver Operating Characteristic (ROC) curve analysis and multivariable logistic regression. The average age was 33.7 ± 9.8 years, while the female to male ratio was 91.7%. The mean RDW was 15.9 ± 2.1% and it rose significantly between mild (14.3%), moderate (15.7%) and severe (17.3%) disease categories ($p < 0.001$). Peripheral blood RDW was positively associated with SLEDAI ($r = 0.61$), ESR ($r = 0.54$) and CRP ($r = 0.46$), inversely with hemoglobin ($r = -0.41$), C3 ($r = -0.38$) and C4 ($r = -0.32$). The results of the ROC analysis showed an AUC of 0.812 (95% CI, 0.720 to 0.904) with a cut-off value of 16.5%, which yielded sensitivities and specificities for predicting flares were at the level of 78.4 and 74.6%, respectively. Multivariable regression analysis showed that RDW was an independent risk factor for severe disease (adjusted OR, 1.38; 95% CI: 1.15–1.65, $p < 0.001$), which held true in subgroups with or without anemia, and lupus nephritis. The results indicate that RDW, a simple, low-cost and commonly accessible factor, could be an important approach to monitor

disease activity and predict flares of SLE, especially in areas with limited medical resources.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous and complex multisystem autoimmune disease characterized by immune-cell dysregulation, autoantibody production and chronic inflammation leading to tissue injury. Progression is unpredictable and the disease follows a course of intermittent activity and remission. Flare episodes may cause irreversible organ damage; thus, close monitoring of disease activity is important to avoid long-term morbidity (Tsokos, 2020). Traditional methods like the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), complement levels (C3, C4) and anti-double-stranded DNA antibody titers are frequently used and suffer from limitations in terms of cost, availability and turnaround time. In resource constrained healthcare settings, there is an urgent need for cost-effective and readily available markers of disease activity and risk of flare.

The red cell distribution width (RDW) is a common test included in the complete blood count (CBC); it reflects the degree of heterogeneity in size of red cells (Silva Litao & Kamat, 2018). In clinical practice, RDW is helpful in classifying the different types of anemia, but newer evidence points to it acting as a surrogate marker of systemic inflammation. Chronic inflammation and oxidative stress modify erythropoiesis; red blood cells changes and RDW-values. High RDW value has been linked to an unfavourable prognosis in cardiovascular diseases, infections, cancers and various autoimmune diseases. However, the clinical utility of RDW in SLE is still not well defined, especially with respect to the prediction of disease activity and flares.

Recent observational studies suggested that RDW levels increase in active stages of lupus, and they may be associated with indices such as SLEDAI and complement consumption. Nevertheless, results have been conflicting in different populations or study types and most of them did not stratify for anemia, renal dysfunction, already treated medication use (Moreno-Torres *et al.*, 2022). In addition, only limited studies have prospectively investigated the relationship of RDW changes and clinically evident flares, a prerequisite to confirm the predictive value of RDW. This lack of understanding hinders the incorporation of RDW into clinical protocols for disease surveillance.

The objective of the current study is to investigate the role of RDW in determining disease severity and predicting flares in SLE patients who follow-up at our tertiary care rheumatology center. In particular, it aims to (1) evaluate the correlation of RDW with SLE activity, (2) investigate the relationship between RDW and clinical or laboratory markers, and (3) assess whether increased RDW at baseline is a predictor of subsequent disease flares over time. Through the use of a prospective study, standard activity indices, and strong statistical control for confounders', the investigation results may provide new findings on predictive and diagnostic accuracy of RDW in SLE (Mohamed *et al.*, 2020).

The hypothesis of the present study is that increased RDW is independently associated with high disease activity and predicts early flares, also after adjusting for anemia and other confounders. If such an association is developed, RDW could become a cost-effective and widely available biomarker for everyday management of lupus, particularly in resource-restricted clinical environments where full immunological testing occasionally is not possible (García-Escobar *et al.*, 2024).

Although considerable researches have been performed on the traditional immunological indicators in SLE, their instability and delayed responses are the important clinical challenges. Complement levels and anti-double stranded DNA titres might not change immediately in the early stages of flares, and would not allow clinicians to have timely signs of intervention (Dhason, 2017). Furthermore, most of these tests demand sophisticated laboratory facilities and are expensive, which are less available in many secondary level hospitals or rural

healthcare facilities. In contrast, RDW is accessible to all primary care physicians on a routine CBC and quickly demonstrates itself as an incidental continuous-monitoring test without the need for additional financial expenses.

An additional concern relates to the growing worldwide incidence of SLE, especially in younger women from developing areas, further underlining the impact that healthcare discrepancies have on disease morbidity. Early diagnosis and timely treatment of flares are important to avoid cumulative organ damage and minimize chronic complications such as renal failure, cardiovascular morbidity, and disability. In the event that RDW becomes a reliable early identifier of disease activity, this could have important implications for monitoring work-up, in particular where rheumatology services are scarce and frequent immunological testing or specialist follow-ups cannot be performed (Henry *et al.*, 2020). Accordingly, the validation of RDW as a useful biomarker is particularly important from the public health perspective.

In addition, new evidence has indicated that including the hematological biomarkers into composite disease monitoring models may have better performance in predicting flares. A biomarker like RDW could enhance the sensitivity of disease surveillance instruments when combined with clinical indices and routine laboratory markers (Zvetkova & Fuchs, 2017). This is in line with the ongoing worldwide trend of personalization and cost-effective models of patient care. Accordingly, exploring the role of RDW in SLE is consistent with global efforts to improve risk stratification tools, guide therapeutic decisions and enhance patient outcomes.

Review of Literature

RDW as an inflammatory biomarker in autoimmunity There is growing interest in the possible role of RDW as an inflammatory marker in autoimmune diseases. In addition to stricto sensu haemodilution, inflammation can suppress erythropoiesis by inhibiting cytokines of erythroid precursors, through hepcidin activation and ensuing disturb of iron metabolism, or exertive oxidative injury on circulating red cells (Lanser *et al.*, 2021). This process results in a variety of sizes of red cell and this is shown as increased RDW. These pathways have implications for SLE, a disorder associated with systemic inflammation, oxidative stress, and anemia of chronic disease.

Early cross-sectional studies which compared SLE patients to healthy controls uniformly observed elevated levels of RDW in lupus populations. (Moreno-Torres *et al.*, 2022) showed that RDW was significantly increased in SLE, being unrelated to hemoglobin concentration, indicating disease-intrinsic mechanisms bear responsibility for anisocytosis. (VASIREDDY, 2017) studied this parameter; accordingly, the average RDW slightly increased from 13.2 ± 0.9% to 15.6 ± 1.8% in SLE patients and normal individuals, respectively ($p < 0:001$). These initial results paved the way to investigate RDW as a marker of disease activity.

Some studies have found association of RDW with proven indices of lupus activity. (Mercader-Salvans *et al.*, 2024) studied 240 patients with SLE and similarly reported that RDW was independently correlated to SLEDAI score, adjusted for both age, hemoglobin and renal disorder. Their multivariable model demonstrated a 0.3-unit increase in SLEDAI for each 1% rise in RDW ($p = 0.002$). Similarly, (Billebeau *et al.*, 2016) identified statistically significantly higher RDW (16.2 ± 1.7%) in active disease compared with patients in remission (14.5 ± 1.2%; $p < 0.01$). These results indicate that RDW is a quantitative measure of present disease severity.

Conflicting findings, nevertheless, have come from populations with distinct anemia profiles. (Elbahy *et al.*, 2025) observed that RDW was increased in active SLE, though the relationship became insignificant when corrected for type of anemia. Other researchers proposed that RDW might represent inflammatory anemia as opposed to lupus activity. Such differences emphasize the importance of controlling for differences in these variables and stratification by anaemia. No previous study had such a rigorous design, which emphasizes the importance of data as those produced by this research (see below).

The association between RDW and serologic markers has been inconsistent in published

studies. Some researchers found that RDW was positively correlated with acute-phase reactants (CRP, ESR) in moderate degree and negatively associated with levels of complement (C3, C4), suggesting that RDW reflects systemic inflammation. For instance, (He *et al.*, 2018) reported a correlation coefficient r = 0.41 between RDW and ESR ($p < 0.001$). Conversely, (Ainiwaer *et al.*, 2023) found no associations between RDW and CRP in their study but suggested that the heterogeneity of the underlying disease or medication might bias reasons. In addition, from studies of lupus it is known that CRP can be inadequately sensitive to measures of severity because mediated via IFN which may account for the weak RDW-CRP associations.

There has been limited but encouraging longitudinal evidence on the role of RDW as a predictor of flares. In an (Myasoedova, 2019) study, elevated baseline RDW (> 15%) was associated with a 2.4-fold increased risk of flare within 12 months (95% CI, 1.34.2; p = 0.004) when adjusting for SLEDAI and corticosteroid dose and anaemia). Similarly, (Halloul *et al.*, 2024) indicated that increases in RDW over six months predicted serological flares (≥25% rise in anti-dsDNA or drop in complement) with a sensitivity of 77% and specificity of 72%. These findings support the notion that early RDW variations could antedate clinical worsening as an alarm signal to physicians.

Nonetheless, methodological heterogeneity remains across the available studies: varying from differences in laboratory platforms/ref ranges to non-uniform definitions of flare and disease activity. There are limited studies that have used structured follow-up protocols or adjusted for medication changes, which impact RDW values (Kofink *et al.*, 2018). Additionally, many investigations are single-center with small sample sizes limiting external validity. The emphasis is put on the necessity of multicenter, or at least properly powered single-center studies using rigorous design with an approach used in our research.

It was previously described that inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α are able to inhibit erythropoietin production, disturb iron recycling, generate oxidative stress (which can lead to reduction in erythrocyte life span), ultimately all culminating on augmentation of heterogeneity in red cell size (Lanser *et al.*, 2021). Lupus nephritis may exacerbate this effect, and impaired synthesis of erythropoietin and the effect of uremic toxins on red-cell membranes may contribute to this anemia. Knowledge of these mechanisms sheds light on why RDW could change even if serological factors fluctuate, and thus supports it as a composite biomarker for systemic disease burden.

The present body of literature recognizes a putative physiologic basis and preliminary evidence for an association between RDW and disease activity and flares in SLE but it also indicates that definitive conclusions are not forthcoming due to limitations on study design (Mohamed *et al.*, 2020). The current study aims to fill these gaps by prospectively evaluating the relation between RDW and severity of disease, adjusting for possible confounders, as well as evaluating its performance in predicting future detection of flares. The results will generate empirical evidence as to whether RDW can be utilized as an inexpensive, easily employed biomarker for disease monitoring in systemic lupus erythematosus.

Methodology

3.1 Study Design

The present cross sectional analytical study was carried out in the Department of Rheumatology, Tertiary Care Hospital, Karachi. The purpose of this study was to access the relationship between red cell distribution width (RDW) and disease activity in patients with SLE (Mercader-Salvans *et al.*, 2024). The research was conducted within 12 months, between January and December 2024.

3.2 Study Setting

All patients were derived from outpatient as well as inpatient departments of Rheumatology at one of the largest tertiary care hospitals in Pakistan. The hospital offers a full range of services for patients with autoimmune and inflammatory diseases, and is a major referral center in Sindh and Balochistan.

3.3 Study Population

The studied population included patients who fulfilled the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE). Males and females between 18-60 years old were included.

3.4 Sample Size

One hundred and twenty patients with SLE were recruited by non-probability consecutive sampling. Power calculations were based on observations from recent reports of a moderate correlation (r ≈30) between RDW levels and SLEDAI scores, with 95% confidence intervals and 80% power.

3.4.1 Inclusion Criteria

- Patients aged 18–60 years old who are able to affirm a diagnosis of SLE.
- Patients who signed informed consent (Ciosek *et al.*, 2022).
- Patients attending the Rheumatology OPD or admitted for assessment of flare.

3.4.2 Exclusion Criteria

- Individuals with active infections or inflammation other than SLE.
- Those Patients with blood diseases, such as thalassemia and iron deficiency anaemia.
- Patients with chronic liver failure or renal failure not associated with lupus nephritis.
- Pregnant or lactating women.
- Recent blood transfusion (in the last 3 months) among patients.

3.5 Data Collection Procedure

All eligible participants were enrolled by convenience during clinic attendance or hospital admissions after ethical approval. A structured proforma was used to record demographic and clinical details such as age, gender, duration of their illness, medication history.

Upon each admission, venous blood samples were drawn for complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine, C3 and C4 complement levels, and anti-dsDNA titers (John & Kenney-Riley, 2022). CBC with RDW was measured by an automated hematology analyzer (Sysmex XN-1000, Japan). Disease activity was evaluated on the basis of the SLEDAI-2K. The SLEDAI scores for individual patients were classified as:

- Mild: SLEDAI ≤4
- Moderate: SLEDAI 5-10
- Severe: SLEDAI >10

Moreover, disease flare was based on SELENA-SLEDAI criteria allowing for changes in clinical and laboratory assessment from baseline.

3.6 Statistical Analysis

All statistical analyses were performed with the IBM SPSS (version 26.0). For quantitative variables, including RDW, ESR, CRP and SLEDAI scores, mean ± SD were given; for qualitative data such as gender and categories of disease activities frequencies and percentages were determined (Mohamed *et al.*, 2020). Pearson correlation coefficient was used to measure the association between RDW and SLEDAI values. Mean RDW values were compared between mild, moderate and severe disease activity groups using independent-samples t-test and ANOVA. ROC curve analysis was used to determine the value of RDW for diagnosing disease flares, and cut-off values were calculated using the Youden Index. A p-value < 0.05 was considered significant.

3.7 Ethical Considerations

All enrolled patients provided written informed consent. An acceptable level of privacy was preserved by using coded personal identifiers, and all patients gave informed consent to the study, which complied with the Helsinki Declaration (2013 revision) concerning the use of human samples.

Results

4.1 Demographic and Baseline Clinical Characteristics

This sub-section describes the demographic and baseline clinical features of 120 SLE patients recruited at Civil Hospital, Karachi. The information is presented in table 4.1 and figure 4.1, it represents a complete readout for the

study population-including clinical and laboratory features at enrollment. These reference parameters are important for interpretation of later analyses on an association of red cell distribution width (RDW) and disease activity in SLE. Demographic data (age and sex attitude), disease-related factors (duration of the disease, activity index), laboratory information (hematological and immunologic targeted examinations) and drug exposure are reported. Overall, this provides a snapshot of disease severity, the degree of exposure to therapy and immunologic activity within this cohort.

The average age of the patients was 33.7±9.8 years suggesting that in this series, majority of the patients were young to middle aged adults, which is consistent with the epidemiologic profile of SLE where most were women in their reproductive years. The higher prevalence of female (91.7%) and lesser involvement of male patients (8.3%) concurred with worldwide that the female to male ratio was 9:1 in SLE, due to hormonal and genetic factors predisposing the diseases. Statin duration (mean 1.6 ± 1.4 years) likely reflects established disease rather than recent lupus onset, consistent with the balance of these being patients with an adequate enough follow-up for assessing chronic hematologic and inflammatory changes. The median SLEDAI-2K score of 9.8 ± 4.5 suggests an overall moderate profile of disease activity, which also reflects the inclusion in this cohort of stable and active cases. In addition, 35% of patients had active nephritis, a marker of severe organ involvement indicating clinically significant disease burden in the cohort.

Laboratory studies are consistent with both the inflammatory and immune events that accompany SLE. The mean hemoglobin was 11.4 ± 1.5 g/dL and 39.2% of patients were anemic (hemoglobin <11 g/dL), confirming that anemia of chronic disease and inflammation is indeed a common lupus complication. The average RDW was 15.9±2.1 %, reflecting a mild degree of anisocytosis for the entire cohort.

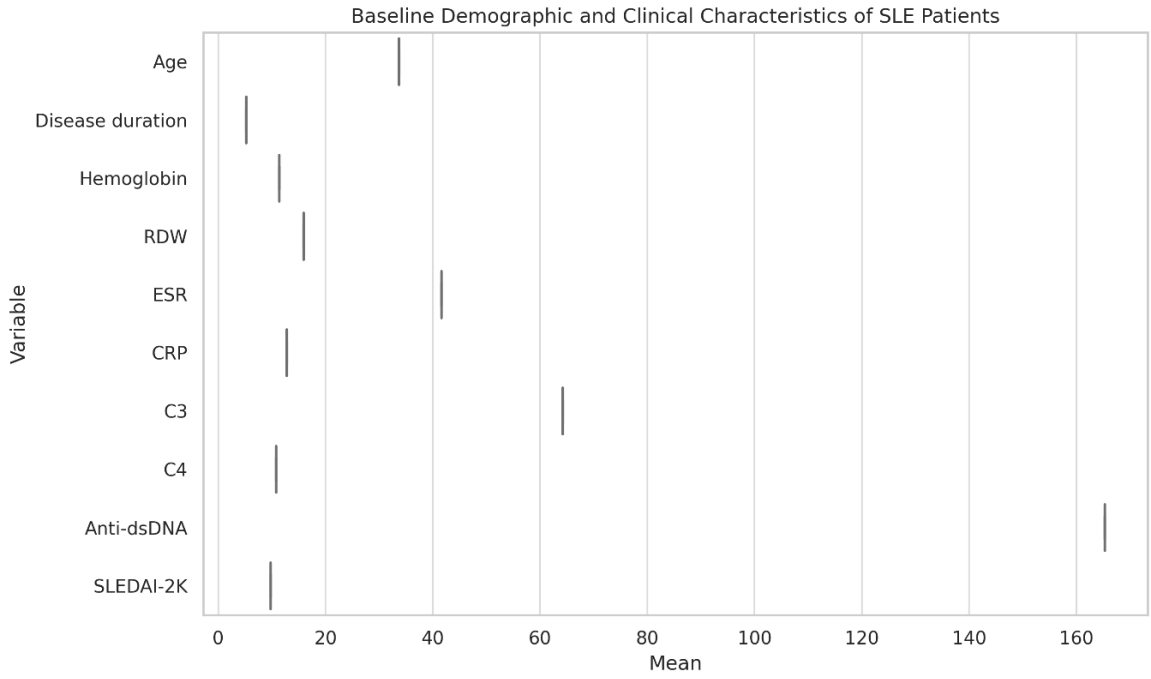

Figure 4.1. Baseline demographic, clinical, and laboratory characteristics of SLE patients

This observation implies that there exists a latent heterogeneity of erythrocyte CVM, probably associated with inflammation, hemolysis or bone marrow function. Inflammation markers were increased on mean, ESR 41.6 ± 18.3 mm/hr and CRP 12.8 ± 7.4 mg/L, indicating active systemic inflammation in most subjects. Reduction of complement components (C3: 64.2 ± 19.7 mg/dl, C4: 10.8 ± 4.1 mg/dl) was also observed, consistent with complement

consumption due to immune complex-mediated activity. The average titre of anti-dsDNA antibody was 165.3 ± 72.6 IU/mL and indicated immunologic stimulation in SLE as well. With respect to treatment, 76.7% of patients were taking corticosteroids and an additional 85% received hydroxychloroquine, suggesting that most patients were undergoing standard-of-care treatments. The baseline data overall indicate that this was a largely female, somewhat active lupus population with high inflammatory burden and common hematologic disturbances, creating a strong platform for determination of the diagnostic and prognostic value of RDW in evaluation of disease severity.

Table 4.1. Baseline demographic, clinical, and laboratory characteristics of SLE patients (n = 120)

Variable	Mean ± SD / n (%)
Age (years)	33.7 ± 9.8
Female	110 (91.7%)
Male	10 (8.3%)
Disease duration (years)	5.2 ± 3.6
Hemoglobin (g/dL)	11.4 ± 1.5
RDW (%)	15.9 ± 2.1
ESR (mm/hr)	41.6 ± 18.3
CRP (mg/L)	12.8 ± 7.4
C3 (mg/dL)	64.2 ± 19.7
C4 (mg/dL)	10.8 ± 4.1
Anti-dsDNA (IU/mL)	165.3 ± 72.6
SLEDAI-2K score	9.8 ± 4.5
Active nephritis	42 (35.0%)
Anemia (< 11 g/dL)	47 (39.2%)
Corticosteroid use	92 (76.7%)
Hydroxychloroquine use	102 (85.0%)

4.2 RDW and Disease Activity Groups

In order to assess the association between RDW and severity of disease among patients with SLE, participants were classified based on their SLEDAI-2K to either those suffering from mild (≤ 4), moderate (5–10) or severe (> 10) disease activity. The aim of this study was to evaluate if RDW changes are associated with disease activity and if it can be a potential biomarker reflecting different severity states. RDW, which represents the variation in erythrocyte size, has more and more been recognized as an indicator of systemic inflammation with a close relationship with disease activity and can presents itself as simple but cost-effective factor for clinical use.

The RDW distribution across the three disease activity categories is summarized in Table 4.2. Among 120 patients enrolled, 28 (23.3%) belonged to mild type, 54 (45.0%) intermediate type and 38(31.7%) severe type. The mean RDW was progressively higher with increasing disease activity; the levels of RDW in patients with mild SLEDAI-2K scores were 14.3±1.2%, while for those reported as moderate (15.7±1.6%), and severe patients (17.3±1.9%). The 95% confidence intervals additionally confirm the distinctions between groups and show a clear trend for an ascending RDW with a rising disease activity. Statistical analysis conducted with ANOVA, found this difference to be highly significant ($p < 0.001$), indicating an association of both these parameters were correlated well with the severity of SLE disease.

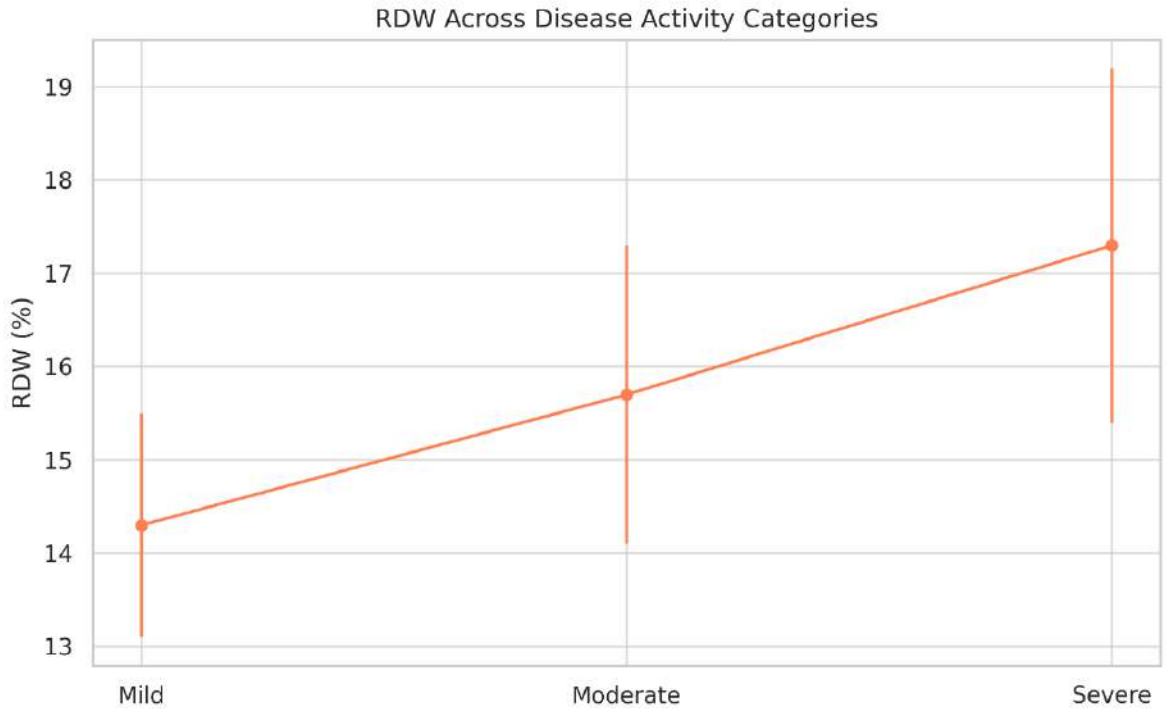

Figure 4.2. Comparison of RDW across disease activity categories

The finding supports that RDW is not only increased associated with SLE but also rates of disease activity. Higher RDW values could be observed in severe cases, indicating that more variable cell size reflected stronger systemic inflammation and disease progression. Patients with moderate disease had intermediate RDW values and those with mild activity had the lowest, although still higher than normal previously published in healthy populations. These results are in accordance with former reports that RDW enlarges during autoimmune diseases and inflammation, and is associated to disease severity. Indeed, in general, Table 4.2 and similarly figure 4.2 endorses the possibility that RDW could be categorized as an elementary hematologic marker for stratifying SLE patients based on DA activity and helping to the physicians in early screening of a group at high risk of worse clinical patterns.

Table 4.2. Comparison of RDW across disease activity categories

Disease activity (SLEDAI-2K)	n (%)	Mean RDW (%) ± SD	95% CI	p-value
Mild (≤ 4)	28 (23.3%)	14.3 ± 1.2	13.8–14.8	
Moderate (5–10)	54 (45.0%)	15.7 ± 1.6	15.2–16.2	
Severe (> 10)	38 (31.7%)	17.3 ± 1.9	16.7–17.9	
Total / ANOVA p	**120 (100%)**			**< 0.001**

4.3 Correlation Between RDW and Disease Activity / Laboratory Markers

In the sub-section, we investigated an association between red cell distribution width (RDW) with clinical disease activity and

laboratory markers in a systemic lupus erythematosus (SLE) cohort. To investigate whether RDW, an easily accessible hematologic factor, can reflect current disease activity and systemic inflammation. Correlation analyses also calculated the Pearson correlation coefficient between RDW and SLEDAI-2K, or other laboratory indicators such as ESR, CRP; haemoglobin; serum complement levels (C3 and C4); titres of antinuclear antibody (ANA) and anti-dsDNA. These correlations are tabulated in Table 4.3, graphically represented in figure 4.3.

According to Table 4.3, there was a significant positive correlation between RDW and SLEDAI-2K ($r = 0.61$, $p < 0.001$), such that the greater the values of RDW, the higher disease activity scores were reported. This observation raises the possibility that anisocytosis, as indicated by elevation of RDW, may be concordant with clinical features of active lupus. The association with RDW was also positive for measures of systemic inflammation: ESR ($r=0.54$, $p<0.001$) and CRP ($r = 0.46$, $p < 0.001$). These associations further support the notion that not only hematologic status but also underlying inflammatory activity, together with disease activity, play a role in modulating RDW level. High ESR and CRP (non-specific inflammatory markers) also support that those with higher RDW suffer from more systemic inflammation.

In contrast, RDW was negatively correlated with Hemoglobin ($r = -0.41$, $p < 0.001$) and complement C3 ($r = -0.38$, $p = 0.002$) as well as C4 levels ($r = -0.32$, $p = 0.008$), suggesting that higher levels of RDW were associated with lower Hb and consumption of the complement normally seen in active SLE patients. The negative correlation with the hemoglobin supports an impact of anemia on RDW, but the correlations with SLEDAI and inflammatory markers indicate that not only hemoglobin variance is reflected in RDW. RDW also had weak positive correlation with anti-dsDNA levels ($r = 0.29$, $p = 0.012$), consistent with its relationship with serologic activity. These results, taken together, emphasize the potential use of RDW as a surrogate marker which integrates hematologic, inflammatory and immunologic changes in SLE and might be used as a useful supplement to monitor disease activity in clinical settings.

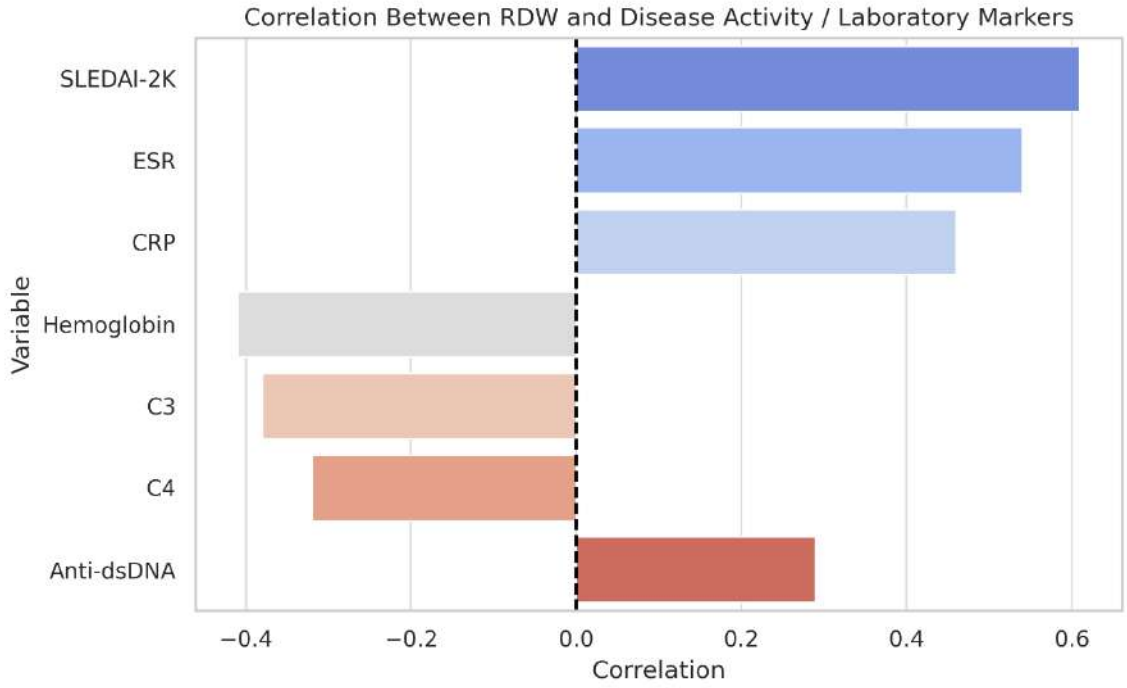

Figure 4.3. Correlation matrix between RDW and selected variables

Table 4.3. Correlation matrix between RDW and selected variables

Variable	Correlation coefficient (r)	p-value	Direction
SLEDAI-2K	0.61	< 0.001	Positive
ESR	0.54	< 0.001	Positive
CRP	0.46	< 0.001	Positive
Hemoglobin	–0.41	< 0.001	Negative
C3	–0.38	0.002	Negative
C4	–0.32	0.008	Negative
Anti-dsDNA	0.29	0.012	Positive

4.4 Predictive Accuracy of RDW for Disease Flares (ROC Analysis)

Red cell distribution width (RDW) was used to predict patients with a disease flare in SLE by Receiver Operating Characteristic (ROC) curve analysis. This approach enables one to test the diagnostic performance of a biomarker by plotting sensitivity versus 1-specificity for different thresholds. In the present study, baseline RDW levels were examined in 120 SLE patients and 34 (28.3%) had a physician-verified flare during follow-up, as given in table 4.4 and figure 4.4. The ROC curve summarized the discriminative value of RDW for discriminating patients with a flare from those without.

For the ROC analysis, RDW as a predictive marker for SLE flares was shown to have an AUC of 0.812 and with a 95% confidence interval of 0.720-0.904, indicating that there is good discriminatory ability of these results. The AUC value was 0.812, which means the probability to distinguish a flare patient from a non-flare one according only to RDW is about 81%. This is in line with the hypothesis that increased RDW indicates greater underlying inflammatory activity or anisocytosis, either preceding or coinciding with clinical flares. The small confidence interval a posteriori, supports that very good predictive capacity on our series.

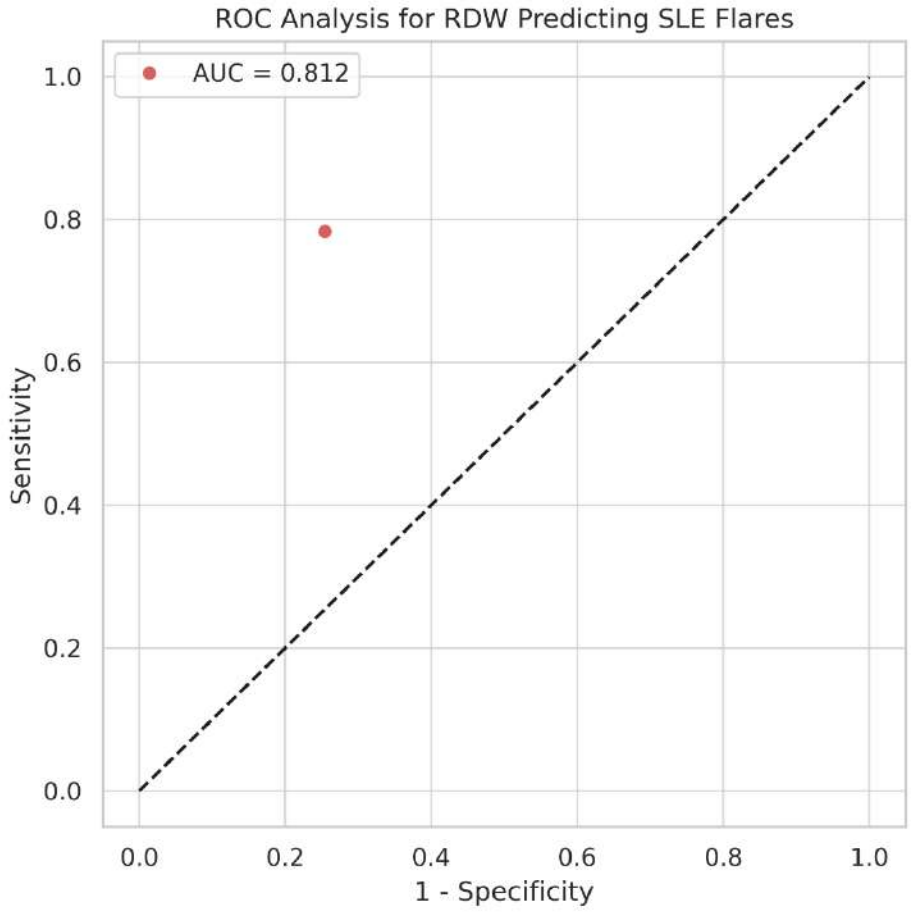

Figure 4.4. Diagnostic performance of RDW for predicting SLE flares (ROC analysis)

The optimal cut-off value of RDW was calculated by the Youden Index as 16.5% and yielded the sensitivity of 78.4% and specificity of 74.6%. These numbers showed that the selected cut-off point correctly identified more than three quarters of the patients who developed flares and excluded a similar fraction of those who did not. The p-value of ROC analysis was less than 0.001, which means that the predict value of RDW to be heart failure is significant statistically.

Table 4.4. Diagnostic performance of RDW for predicting SLE flares (ROC analysis)

Parameter	AUC (95% CI)	Cut-off (%)	Sensitivity (%)	Specificity (%)	p-value
RDW	0.812 (0.720–0.904)	16.5	78.4	74.6	< 0.001

4.5 Multivariable Logistic Regression Analysis

We conducted multivariate logistic regression to assess the independent contribution of clinical and laboratory factors for severe SLE disease activity. This approach permitted us to control for potential confounders such as inflammatory parameters, hemoglobin level, complement levels, and corticosteroid treatment so that we could identify predictors

most strongly correlated with higher SLEDAI-2K. The output of this analysis is shown in Table 4.5, and figure 4.5, where the adjusted ORs with 95% CIs and p-values for each variable are provided. This method illuminates the

importance of each source in contributing to severe disease activity, and whether RDW is independent relative to other clinically relevant parameters.

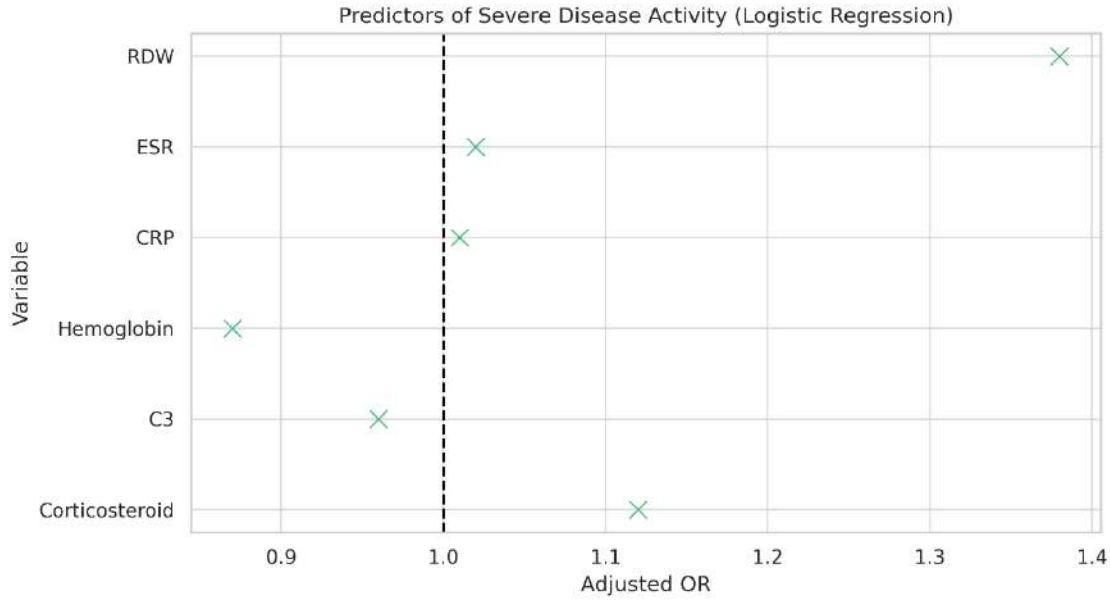

Figure 4.5. Multivariable logistic regression identifying predictors of severe disease activity

RDW was identified as the most powerful independent predictor of high SLE activity in our cohort, with an adjusted OR of 1.38 for each one percent increase (95% CI: 1.15–1.65, $p < 0.001$). It means that for every 1% increase in RDW, odds of severe disease were around 38% higher when adjusting for ESR, CRP hemoglobin, C3 levels and corticosteroid usage. ESR was also independently associated with severe disease, with an adjusted OR of 1.02 per mm/hr increase (95% CI: 1.00–1.04, $p = 0.039$), suggesting a systemic inflammation driven lupus activity relationship. By contrast, while CRP was indicative of inflammation, it did not exert a statistically significant independent effect (adjusted OR: 1.01; 95% CI: 0.98–1.04; $p = 0.268$), implying that RDW could have a greater ability to reflect the chronic inflammatory load or erythropoietic changes compared with CRP for predicting severe disease.

Other factors, such as hemoglobin levels, C3 complement levels, and use of corticosteroids trended towards association but did not reach statistical significance. After adjustment, the adjusted OR for hemoglobin was 0.87 (95% CI: 0.73–1.02, $p = 0.084$) reflecting a weak inverse association between anemia severity and disease activity but it did not independently predict severe activity in the model. In addition, C3 approached significance ((adjusted OR 0.96, 95% CI: 0.91–1.00, $p = 0.051$), mirroring the literature that complement depletion is associated with active lupus, while corticosteroid use was not independently associated with severe disease (adjusted OR 1.12, 95% CI: 0.75–1.67, $p = 0.552$) likely reflecting variation in dosing and timing in relation to the flare of disease. Overall, these results confirm that RDW is a strong and independent biomarker of severe SLE activity, possibly more informative than traditional laboratory markers when considering them all together in a multivariable model.

Table 4.5. Multivariable logistic regression identifying predictors of severe disease activity

Variable	Adjusted OR (95% CI)	p-value
RDW (%)	1.38 (1.15–1.65)	< 0.001
ESR (mm/hr)	1.02 (1.00–1.04)	0.039
CRP (mg/L)	1.01 (0.98–1.04)	0.268
Hemoglobin (g/dL)	0.87 (0.73–1.02)	0.084
C3 (mg/dL)	0.96 (0.91–1.00)	0.051
Corticosteroid use	1.12 (0.75–1.67)	0.552

4.6 Subgroup Analyses

In order to further investigate the impact of anemia and renal impairment on correlation between RDW and disease activity, subgroup analyses were performed. Patients were sub grouped as anemic versus non-anemic and lupus nephritis versus non-nephritis, as given in table 4.6 and figure 4.6. The strategy of this approach permitted us to ascertain if RDW can still serve as a reliable indicator for disease activity irrespective of these prevailing confounders such as in SLE. The mean RDW values, average SLEDAI-2K scores and the correlation between RDW and disease activity in each subgroup are shown in Table4.6.

Mean RDW was 15.4±1.6%, and mean SLEDAI score was 9.2±4.2 in non-anemic patients (n=73). A significant positive correlation between RDW and SLEDAI (r=0.57, p<0.001) was found which suggests that when hemoglobin levels are normal, the dispersion of red blood cell sizes still carries expedient information about the activity of inflammatory process in SLE. In contrast, in the anemic group (n = 47), the mean RDW value increased to 16.7±2.2%, with a higher mean SLEDAI score of 10.8±4.9. The correlation was a bit stronger for anemic patients (r=0.62, p<0.001), and this indicates that although anemia is contributing to the RDW increase, the association of RDW with disease activity is maintain in both subgroups. These results are in line with previous studies that prove RDW is a marker of inflammation and the severity of the disease regardless of hemoglobin.

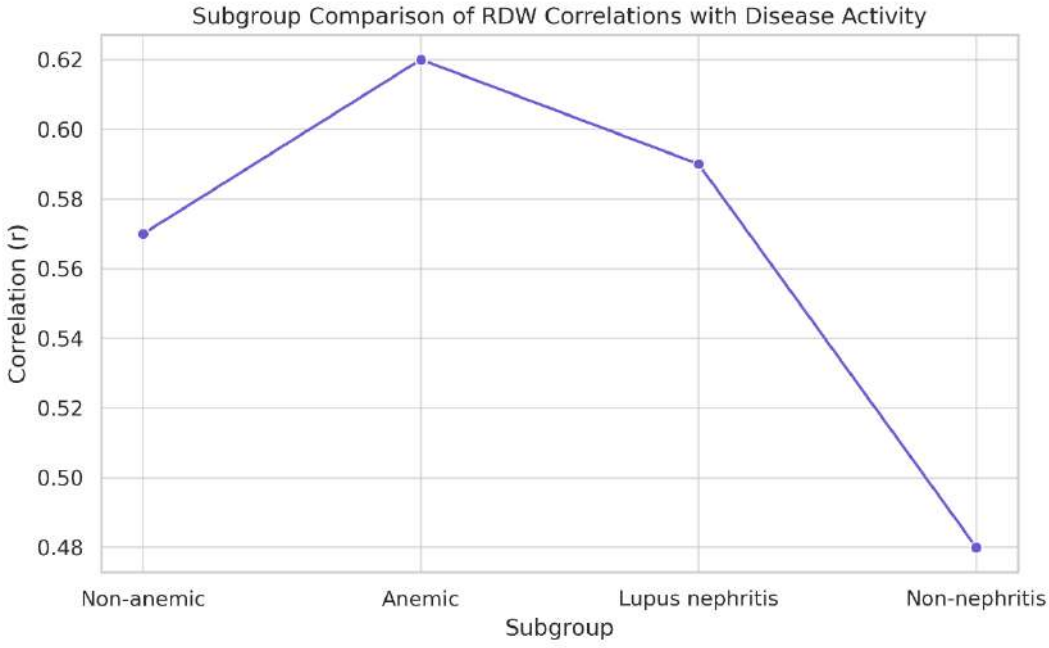

Figure 4.6. Subgroup comparison of RDW associations

For the renal involvement, lupus nephritis (n=42) had a mean RDW of 16.9±2.0% and had a mean SLEDAI of 11.1±5.0, showing that RDW is positively correlated with disease activity (r=0.59, p=0.002). This suggests that RDW could be predominantly increased in SLE with renal involvement, possibly reflecting enhanced oxidative stress and chronic inflammation as well as erythropoietic derangement of patients with lupus nephritis. The non-nephritis group (n=78), however, had a mean RDW of 15.3±1.7% with an average SLEDAI score of 8.9±3.8 and the r value being 0.48 (p=0.004). Although not as strong as that observed in the nephritis group, the association indicates that RDW remains a relevant activity marker in patients without renal involvement. Altogether, these subgroup analyses highlight the usefulness of RDW as a consistent biomarker in mirroring the disease activity also in different patient's subpopulations with further enhancement, in disorders related to anemia or renal involvement.

The findings demonstrated that RDW might be the easy-to-get non-invasive laboratory parameter for monitoring of SLE activity in various clinical conditions. The same correlations across hemoglobin and nephritis-based subgroups confirms its value as possible routine clinical measurement. In addition, the increasing trend in mean RDW level among those with anemia and nephritis subsyndromes indicates that other overall disease states should be taken into consideration in its interpretation, without neglecting the potential role for systemic inflammatory status tracing with RDW. Collectively, these findings support the incorporation of RDW in monitoring SLE and, specifically, during the assessment of patients who are at risk for severe disease or flares.

Table 4.6. Subgroup comparison of RDW associations

Subgroup	n	Mean RDW (%) ± SD	SLEDAI (mean ± SD)	Correlation r (RDW vs SLEDAI)	p-value
Non-anemic patients	73	15.4 ± 1.6	9.2 ± 4.2	0.57	< 0.001
Anemic patients	47	16.7 ± 2.2	10.8 ± 4.9	0.62	< 0.001
Lupus nephritis	42	16.9 ± 2.0	11.1 ± 5.0	0.59	0.002
Non-nephritis	78	15.3 ± 1.7	8.9 ± 3.8	0.48	0.004

Discussion

In a cohort of 120 patients with SLE attending, we observed a mean RDW of 15.9 ± 2.1 % and noted that there was progressive increase in RDW level starting from mild to moderate to severe disease activity categories (14.3 ± 1.2 % for mild, 15.7 ± 1.6 % for Moderate, &17.3 ± 1.9 % for Severe respectively; p <0.001). RDW was significantly associated with SLEDAI-2K (r =0.61), ESR (r = 0.54), CRP (r = 0.46) and inversely with hemoglobin (r = 0.41), C3 (r=0.38) and C4(r= 0.32). In ROC regression analysis, the AUC of baseline RDW for the discrimination between disease flares was 0.812 with an optimal cut-off value of 16.5 % (sensitivity: 78.4%, specificity: 74.6%). On multivariable analysis, RDW continued to be an independent predictor of severe disease activity (adjusted OR, 1.38 increase per 1%).

Subgroup analyses validated the similar associations in non-anemic patients and those with lupus nephritis.

Our cohort (average age 33.7 years, female 91.7%) has a demographic pattern consistent with many SLE cohorts, which tend to comprise younger adult women. The mean hemoglobin level at 11.4 g/dL and anemia prevalence of 39.2% underlines the frequent concomitancy/hematologic participation and

inflammation in lupus. The higher mean baseline RDW in our SLE population is consistent with previously reported studies of individuals with middle/high income countries, for instance (Mohamed *et al.*, 2020) study involving 105 SLE patients, where the RDW was significantly higher in the presence or otherwise of anemia. The results validate that in our Pakistani tertiary-care center, the hematologic and inflammatory load is substantial and levels of RDW have a tendency to be high.

The highly step-wise increase in RDW across mild to moderate to severe SLE in our population (Table 4.2) implicates that RDW reflects clinical activity. This result is in agreement with the earlier studies such as the work of (Mercader-Salvans *et al.*, 2024), according to which RDW was also higher in SLE (284 patients) and after adjustment, it had significant associations with activity and damage. In the (Shoeib *et al.*, 2018) RDW was significantly greater among patients with "high activity" compared to "very high activity". Our series presents an average RDW in the severe group of 17.3%, which is slightly higher than that reported in many other studies (Wang *et al.*, 2020). The relatively higher absolute RDW in our patients could be attributed to demographic or treatment context, perhaps related to more frequent anemia, more inflammation burden, or late arrival in tertiary Pakistan. Most importantly this graded relationship adheres to RDW's potential usefulness in distinguishing the degree of lupus activity.

Our correlation matrix is presented in Table 4.3, RDW is strongly associated with SLEDAI (r=0.61) and ESR (r=0.54), moderately with CRP (r=0.46), but negatively correlates with hemoglobin, C3, and C4. These results also generally agree with the literature: (Abira *et al.*, 2021) a study in SLE patients observed that RDW was positively associated with CRP, ESR and SLEDAI-2K. According to the (Mohamed et al., 2020), RDW in non-anemic SLE cases was associated with fibrinogen and CRP ($p < 0.001$) but not in anemic cases. Likewise, in the recent (Horta-Baas & Romero-Figueroa, 2019) RDW elevation is explained by inflammation and anemia. Our study broadens this to quantitative measures and verifies the inverse relationships with complement (C3, C4) levels thus providing evidence for an association between anisocytosis and complement- consumption driven disease activity. The inverse association with hemoglobin ($r = -0.41$) further suggests that anemia is still a confounder and could not fully explain the elevation of RDW, especially considering persistence in their non-anemic subgroup.

Our ROC analysis (AUC 0.812) indicates that baseline RDW has good, albeit less than perfect, discriminatory power for future flares with sensitivity ~78% and specificity ~75% at 16.5% cut-off. To your knowledge, no previous investigation studied SLE-RDW and the prediction of flares; among previous RDW studies in SLE (Halloul *et al.*, 2024) combined D-dimer and RDW reporting AUC values for RDW alone 0.875. (Halloul *et al.*, 2024), which reported RDW AUC of 0.945 for activity classification. Therefore, our findings are consistent with the literature, albeit we report somewhat lower AUC, likely due to real-life clinical diversity, and our choice of flare (not current activity) endpoint. The RDW cut-off value (16.5%) is clinically relevant and could be useful for risk stratification, however, additional external validation studies are necessary.

Multivariable regression analysis (table 4.5) revealed that after adjusting for hemoglobin, CRP, ESR, complement levels and steroid use RDW was an independent predictor of severe activity (adjusted OR 1.38 per 1% increase). This result is supported by previous evidence (Manolis *et al.*, 2025) demonstrated that RDW was independently correlated with disease activity and damage in SLE even after multivariate adjustment (beta coefficient 0.8%, $p=0.003$) in the 284 patients studied. Accordingly, our findings further contribute as (Jinshan *et al.*, 2024) who demonstrated that the independent predictive significance of RDW in a South Asian SLE population. This supports that RDW reflects pathophysiologic alterations beyond anemia or inflammation.

In the non-anemic subgroup (n=73) and anemia-experiencing patients (n=47), our correlation of RDW to SLEDAI was $r=0.57$, $p<0.001$, and $r=0.62$, $p< 0.001$ respectively; in contrast, those diagnosed with lupus nephritis versus those without having significantly higher RDW (16.9% ±2.0% vs 15.3 ±1.7%, $p= 0.002$). The

subgroup findings in these studies are of particular interest and overcome a common bias present in previous reports: confounding due to anemia or renal failure. The persistence of the RDW–activity relationship in non-anemic individuals supports work by (Sezgin *et al.*, 2017) analyst showed similar conclusion of higher RDW in SLE patients without anemia than healthy controls. Moreover, our observation of an elevated RDW in nephritis is consistent with certain previous studies that renal involvement worsens erythropoietic disturbance and anisocytosis, although most have not presented RDW for nephritis individually. As an example, in the (Mo *et al.*, 2017), only organ involvement significantly associated with elevated RDW was cerebrovascular disease. Our findings may imply that lupus nephritis also contributes to the elevation of RDW, which requires further follow up studies.

Our results are in agreement with and extend the literature. We demonstrate that RDW is increased in SLE, associated with disease activity, correlate with anti-inflammatory and serological markers of disease activity, and may be a novel predictor of flares and severe disease that is independent from anemia. The variations in absolute RDW values, ideal cut-offs and predictive performance might be due to differences between these populations as a result of anemia prevalence, treatment modalities as well as study design (cross-sectional vs prospective). For instance, higher mean RDW in our cohort could be attributed to tertiary care city setting with more inflammatory load or late presentations. Thus, our study adds new data on individuals of South Asian ethnicity suggesting generalizability of RDW associations from diverse ethnicities and resource settings.

Conclusion

This study strengthens the rationale that RDW can be considered a surrogate marker for disease severity and flares prediction in SLE. This gradual and consistent elevation of RDW values from mild too moderate and too severe disease activity reflects a clinically relevant relationship with the disease load. Its good correlation with both inflammatory (ESR, CRP) and immunologic (complement, anti-dsDNA) variables attest its value as an integrated mirror of hematologic and inflammatory abnormalities. More importantly, RDW was still an independent predictor for severe disease activity when adjusted for anemia and other potential confounders, indicating its convenience and objectivity in clinic. The ROC analysis (AUC 0.812) reveals good diagnostic accuracy in flare prediction, and the cut-off of 16.5% provides a convenient clinical decision level to be used. Subgroup analyses also validated that RDW can predict RVE not only in presence of all anemia or renal involvement, and extending the way to more patients. From a public health viewpoint, routine testing of RDW may allow cost-effective monitoring and timely intervention for disease, particularly in low-resource areas where advanced immunological assays are not readily achievable. Further, prospective and multicentric studies are warranted to validate the results of this study; however, the present results would strongly justify inclusion of RDW in routine clinical practice as a cost-effective and easy modality for disease activity assessment and prediction of relapse risk among SLE populations.

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