Red blood cell distribution width as a surrogate biomarker of damage and disease activity in patients with systemic lupus erythematosus

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Abstract

Objective

Red blood cell distribution width (RDW) is a measure of variability in mean corpuscular volume. Alterations in RDW can be observed in a variety of human disorders, including inflammatory, cardiovascular, and hepatic or renal diseases. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect virtually any organ in the body. In this work, our objective was to analyse how a complete characterisation of disease characteristics in a large series of patients with SLE is related to RDW values.

Methods

284 patients with SLE and 181 age- and sex-matched healthy controls were recruited. Complete blood count including RDW was assessed. Multivariable analysis was performed to analyse the relationship between RDW and SLE disease characteristics, including composite scores of disease activity and damage.

Results

After multivariable adjustment, RDW was higher in patients with SLE compared to controls (beta coefficient 0.8 [95% confidence interval: 0.3–1] %, p=0.003). Several disease characteristics, such as the presence of extractable nuclear antibodies and antiphospholipid syndrome, and the use of prednisone and azathioprine, were significantly associated with higher levels of RDW after adjustment for confounders. Of note, cumulative disease damage and disease activity scores were associated with higher RDW values after controlling for covariates.

Conclusion

RDW may serve as a surrogate biomarker of accrual disease damage and activity in patients with SLE.

Key words

red blood cell distribution width, systemic lupus erythematosus

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Introduction

Red cell distribution width (RDW) is a measure of the variability in mean corpuscular volume, which is reflected in the degree of anisocytosis observed in peripheral blood smears (1). RDW is calculated as the coefficient of variation or the standard deviation of the distribution curve of mean corpuscular volume (2). The typical reference range falls between 12% to 15% (3). A high RDW indicates a significant variation in the sizes of red blood cells. Consequently, markedly elevated RDW may be observed in conditions such as iron deficiency anemia, transfusion-related anemia, myelodysplastic syndromes, and haemoglobinopathies. In contrast, a normal to slightly elevated RDW can be seen in thalassaemia trait and anaemia of chronic disease or inflammation. However, RDW cannot replace serum ferritin or iron studies, or other tests to distinguish between these conditions. Similarly, abnormalities in the RDW curve may suggest specific types of anaemia. For example, an extension of the curve to the left (indicating a red blood cell population with smaller volumes) may indicate the presence of microspherocytes or schistocytes. In contrast, a shoulder to the right on the curve usually corresponds to an extremely large population of red blood cells or reticulocytes and may indicate red blood cell agglutination (4).

Recent evidence suggests that disruptions in RDW can be observed in a range of human disorders, including cardiovascular disease, venous thromboembolism, cancer, diabetes, community-acquired pneumonia, chronic obstructive pulmonary disease, liver, and kidney failure, and various acute or chronic conditions (5). It is particularly noteworthy that RDW is increasingly recognised as a potent and independent predictor of mortality in the general population (6–9). However, it remains unclear whether an elevated RDW value constitutes a true risk factor or simply reflects a secondary consequence of underlying biological and metabolic differences. No definitive conclusions have yet been reached on this matter.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of uncertain origin that can affect virtually any organ in the body. Immune irregularities, particularly the production of numerous antinuclear antibodies, are a prominent feature of the disease (10). Patients present with various clinical manifestations, ranging from mild joint and skin problems to severe renal, haematological, or central nervous system complications (11). The clinical diversity of SLE and the absence of definitive biomarkers represent a diagnostic enigma for physicians (12). Haematologic abnormalities are common in SLE, and all three blood cell lines can be affected, including anaemia, leukopenia, and thrombocytopenia (13). These haematological abnormalities may be a manifestation of SLE, related to another concomitant disease and/or caused by SLE treatment.

In the present work, our objective is to analyse how disease characteristics are related to RDW in a well-characterised series of patients with SLE.

Material and methods

Study participants

This was a cross-sectional study that included 465 individuals, 284 of them diagnosed with SLE and 181 controls matched by sex and age. All patients with SLE were 18 years or older, had a clinical diagnosis of SLE, and met ≥4 American College of Rheumatology (ACR) classification criteria for SLE (14). They had been diagnosed by rheumatologists and were periodically followed up in rheumatology outpatient clinics. Patients taking prednisone, at an equivalent dose ≤10 mg/day, were allowed to participate, as glucocorticoids are often used in the treatment of SLE. Controls were community-based and recruited by general practitioners in primary care settings. Controls with a history of any inflammatory rheumatic disease were excluded. None of the controls were receiving glucocorticoids. None of the patients and controls had any haematological disease such as aplasia or myeloproliferative or myelodysplastic disorders, nor were they under iron supplementation. The research was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review

Committee of the Hospital Universitario de Canarias and the Hospital Universitario Doctor Negrín (both in Spain), and all individuals gave written informed consent (approval no. 2021-023-1).

Data collection

Individuals included in the study completed a cardiovascular risk factor and medication use questionnaire and underwent a physical examination. Weight, height, body mass index, abdominal circumference, and systolic and diastolic blood pressure (measured with the participant in a supine position) were assessed under standardised conditions. Information regarding smoking status and hypertension treatment was obtained from the questionnaire. Medical records were reviewed to determine specific diagnoses and medications. SLE disease activity and damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) (15) and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR Damage Index -SDI-) (16), respectively. For the present study proposal, the SLEDAI-2k index was divided into none (0 points), mild (1–5 points), moderate (6–10 points), high (11–19) and very high activity (>20) as previously described (17). Additionally, carotid ultrasound was performed in patients with SLE to evaluate carotid intima-media wall thickness (cIMT) in the common carotid artery and to identify focal plaques in the extracranial carotid according to the Mannheim consensus definitions (12, 13). Dyslipidaemia was defined if one of the following was present: total cholesterol >200 mg/dl, triglycerides >150 mg/dl, HDL cholesterol <40 in men or <50 mg/dl in women, or LDL cholesterol >130 mg/dl. The Sysmex-XN automated blood cell analyzer (Sysmex, Kobe, Japan) was used to measure blood cells counts. The Sysmex instrument uses the standard deviation, and not the coefficient of variation, of the mean corpuscular volume distribution curve for the calculation of RDW.

Table I. Characteristics of the patients with systemic lupus erythematosus and controls.

	Controls (n=181)	SLE patients (n=284)	*p*
Age, years	50 ± 12	50 ± 12	0.70
Female, n (%)	162 (90)	261 (92)	0.38
Body mass index, kg/m^2	30 ± 3	28 ± 6	**<0.001**
Cardiovascular co-morbidity			
Smoking, n (%)	32 (17)	69 (24)	0.092
Diabetes, n (%)	28 (16)	18 (6)	**<0.001**
Hypertension, n (%)	51 (28)	111 (39)	**0.015**
Obesity, n (%)	49 (27)	84 (30)	0.56
Dyslipidaemia, n (%)	140 (77)	197 (69)	0.060
Statins, n (%)	44 (24)	72 (25)	0.80
Aspirin, n (%)	9 (11)	80 (29)	**0.001**
Carotid intima media thickness, microns		628 ± 109	
Carotid plaque, n (%)		99 (36)	
SLE related data			
Disease duration, years		16 (7-24)	
CRP, mg/dl		2.0 (0.8-4.4)	
SLICC-DI		1 (0-2)	
SLICC-DI ³1, n (%)		191 (68)	
SLEDAI-2K		2 (0-4)	
SLEDAI categories, n (%)			
No activity, n (%)		109 (40)	
Mild, n (%)		107 (39)	
Moderate, n (%)		41 (15)	
High, n (%)		10 (4)	
Very high, n (%)		4 (1)	
Auto-antibody profile			
Anti-DNA positive, n (%)		151 (67)	
Anti-ENA positive, n (%)		164 (69)	
Anti-SSA, n (%)		55 (35)	
Anti-SSB, n (%)		36 (21)	
Anti-RNP, n (%)		64 (28)	
Anti-Sm, n (%)		24 (10)	
Anti-ribosome		13 (9)	
Anti-nucleosome		32 (22)	
Anti-histone		22 (15)	
Antiphospholipid syndrome, n (%)		43 (16)	
Antiphospholipid autoantibodies, n (%)		61 (32)	
Lupus anticoagulant, n (%)		51 (28)	
ACA IgM, n (%)		22 (11)	
ACA IgG, n (%)		39 (20)	
Anti beta2 glycoprotein IgM, n (%)		19 (10)	
Anti beta2 glycoprotein IgG, n (%)		28 (15)	
Current prednisone, n (%)		140 (50)	
Prednisone, mg/day		5 (5-7.5)	
Hydroxychloroquine, n (%)		194 (69)	
Methotrexate, n (%)		31 (11)	
Mycophenolate mofetil, n (%)		31 (11)	
Azathioprine, n (%)		43 (15)	
Rituximab, n (%)		8 (3)	
Belimumab, n (%)		8 (3)	

Data represent mean ± SD or median (interquartile range) when data were not normally distributed. BMI: body mass index; C3 C4: complement; CRP: C reactive protein; ACA: anticardiolipin; ANA: antinuclear antibodies; ENA: extractible nuclear antibodies. Carotid ultrasound was not available for controls.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. SLEDAI categories were defined as: 0, no activity; 1-5 mild; 6-10 moderate; >10 high activity, >20 very high activity
SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index. Dyslipidaemia was defined if one of the following was present: total cholesterol >200 mg/dl, triglycerides >150 mg/dl, HDL cholesterol <40 in men or <50 mg/dl in women, or LDL cholesterol >130 mg/dl. Significant *p*-values ae given in bold.

Statistical analysis

Demographic and clinical characteristics of patients with SLE were presented as mean (standard deviation) or percentages for categorical variables. For continuous variables that did not follow a normal distribution, data were reported as median and interquartile range (IQR). Univariable differences

Table II. Multivariable analysis of the differences between patients with systemic lupus erythematosus and controls in haematological cell count.

	Controls (n=181)	SLE patients (n=284)	*p*	Beta coef. (95%CI)	*p*
	Univariable			Multivariable	
Red blood cells, x10e6 / mm3	**4.69 ± 0.43**	**4.44 ± 0.43**	**<0.001**	**-0.2 (-0.3-(-0.1))**	**<0.001**
Haemoglobin, g/dL	**13.7 ± 1.3**	**13.2 ± 1.3**	**<0.001**	**-0.4 (-0.8-(-0.08))**	**0.017**
Haematocrit, %	**42.1 ± 3.4**	**40.1 ± 3.7**	**<0.001**	**-2 (-3-(-0.9))**	**<0.001**
Mean corpuscular volume, fL	89.8 ± 5.5	90.6 ± 6.1	0.20	0.2 (-1-2)	0.76
Mean corpuscular haemoglobin, pg	**29.3 ± 2.2**	**29.9 ± 2.5**	**0.007**	0.5 (-0.1-1)	0.12
Mean corpuscular haemoglobin concentration, g/dl	**32.5 ± 1.1**	**32.9 ± 2.1**	**0.047**	0.3 (-0.3-0.8)	0.33
Red cell distribution width, %	13.4 ± 1.5	13.8 ± 2.1	0.054	**0.8 (0.3-1.3)**	**0.003**
Leucocytes / mm^3	**7356 ± 1972**	**6042 ± 2276**	**<0.001**	**-1351 (-1933-(-769)**	**<0.001**
Neutrophils / mm^3	**4019 ± 1496**	**3524 ± 1733**	**0.002**	**-587 (-1037-(-137))**	**0.011**
Lymphocytes / mm^3	**2479 ± 875**	**1787 ± 957**	**<0.001**	**-634 (-871-(-396))**	**<0.001**
Monocytes / mm^3	582 ± 169	548 ± 208	0.064	-36 (-89-17)	0.19
Eosinophils / mm^3	**191 (110-293)**	**70 (30-140)**	**<0.001**	**-119 (-154-(-84))**	**<0.001**
Basophils / mm^3	**43 (32-61)**	**40 (20-100)**	**<0.001**	19 (-8-46)	0.17
Platelets x10e3 / mm^3	**270 ± 60**	**237 ± 79**	**<0.001**	**-29 (-49-(-97))**	**0.004**

In the multivariable analysis, controls is considered the reference variable. Significant *p*-values ae given in bold. fL: femtoliters. Multivariable analysis is adjusted for body mass index, smoking, diabetes, hypertension, dyslipidaemia, and aspirin intake.

between patients and controls were assessed through Student's t-test, the Mann-Whitney U-test, Chi squared test or Fisher's exact test according to the normal distribution or the number of subjects. Differences between patients and controls regarding haematological counts cells were assessed through multivariable linear regression analysis using controls as the reference variable. The association between disease-related data and RDW was examined using multivariable linear regression analysis, with adjustments made for confounding variables. Confounders were selected from demographics and traditional CV risk factors if their p-values were below 0.20 in the univariable analysis of haematological scores. All analyses were conducted using Stata software, version 17/SE (StataCorp, College Station, TX, USA), with a two-sided significance level set at 5%. A *p*-value less than 0.05 was considered statistically significant.

Results

Demographic and disease-related data of patients with systemic lupus erythematosus

Table I shows an overview of the characteristics of the 284 patients and 181 age- and sex-matched controls included in the study. The majority of participants were women, constituting more than 90% of both study populations, with a mean age of 50±12 years in both groups. The average body mass index was slightly lower in SLE patients compared to the control group, and this difference was statistically significant. Classic cardiovascular risk factors were prevalent in both the patient and control groups. While diabetes was significantly more common among controls, hypertension was more common among subjects with SLE. Furthermore, there were no significant differences in statin use between the two groups, but aspirin use was higher in SLE patients. The cIMT in patients with SLE was 628±109 microns and carotid plaques were present in 36% of them (Table I). The median duration of SLE disease was 16 years (IQR 7-24). The majority of SLE patients had no disease activity (40%) or had mild to moderate activity (39%), as indicated by their SLE-DAI-2K scores. The SLICC-SDI index yielded a median of 1 (IQR 0-2). Notably, 68% of patients had a SLICC-SDI score of 1 or higher. Approximately half of the patients (50%) were taking prednisone, with a median daily dose of 5 mg/day (IQR 5–7.5). At the time of recruitment, 67% of patients tested positive for anti-DNA antibodies and 69% tested positive for anti-ENA antibodies, with anti-SSA being the most detected autoantibody (35%). Sixty-nine percent of patients were using hydroxychloroquine at the time of the study. Other disease-modifying anti-rheumatic drugs included methotrexate (11%) and azathioprine (15%). Additional information related to SLE is shown in Table I.

Multivariable analysis of the differences between patients and controls in haematological count cells

Complete blood cell counts values for patients with SLE and controls are shown in Table II. Many differences were observed after multivariable analysis. Regarding white blood cells, leukocytes, neutrophils, lymphocytes, and eosinophils, they were significantly lower in patients with SLE compared to controls. This was not the case for monocytes and basophils, for which no significant differences were found. Similarly, the number of platelets was significantly lower in SLE patients compared to controls. Of note, after adjustment, total red blood cell count, haemoglobin, and haematocrit were significantly lower in SLE patients compared to controls. However, RDW was found to be higher in SLE patients compared to healthy subjects after multivariable analysis (beta coefficient 0.8 [95% confidence interval: 0.3–1]%, *p*=0.003). (Table II).

Demographic and disease characteristics in relation to RDW

The age and BMI of SLE patients were positively and significantly related to RDW values. The same occurred with

certain cardiovascular risk factors, such as diabetes, obesity, and the use of statins. Regarding the characteristics of the disease, several of them showed an association with RDW. In this sense, being positive for ENA in any of its types, the presence of a history of antiphospholipid syndrome and the use of prednisone and azathioprine were significantly associated with higher RDW values. Remarkably, the disease damage index SLICC-SDI was associated with higher RDW values both when considered continuous and binary. Disease activity score SLEDAI-2K also showed a significant and positive relationship with RDW. However, this relationship was found only when this score was assessed continuously but not when it was analysed categorically (Table III).

The SLICC and SLEDAI scores are a sum of different aspects of SLE. For this reason, given that both showed a significant association with the RDW, we analysed the relationship of their items, one by one, with the RDW. Regarding SLEDAI (Table IV), the items that revealed significant relationships with RDW were the presence of urinary casts, haematuria, mucosal ulcers, fever, and low complement. With respect to the SLICC-SDI, any cataract ever, pulmonary hypertension, angina or coronary artery bypass, venous thrombosis, infarction or bowel resection, diabetes and having 1 point or more in the skin domain were the items that revealed significant relationships with RDW (Table V).

Discussion

Our series of patients with SLE is the largest and best characterised in which the relationship of RDW with the characteristics of the disease has been studied. As our results show, RDW is higher in patients with SLE compared to controls. Furthermore, this haematological parameter is independently related to several characteristics of the disease, including its damage and activity.

RDW has attracted some attention in previous reports. In a previous work in 105 patients with SLE and 60 healthy people matched in age and sex, the level of RDW in the active group with SLE was significantly higher than in

Table III. Relationship of demographic and disease characteristics to red blood cell distribution width.

	Red Cell Distribution Width, %				
	Univariable beta coef. (95%), *p*			Adjusted	
Age, years	**0.03**	**(0.004-0.05)**	**0.022**		
Female	0.5	(-0.5-1)	0.37		
Body mass index, kg/m^2	**0.1**	**(0.03-0.1)**	**0.001**		
Cardiovascular co-morbidity					
Smoking	-0.1	(-1-0.5)	0.66		
Diabetes	**1**	**(0.2-2)**	**0.023**		
Hypertension	0.4	(-0.1-1)	0.093		
Obesity	**1**	**(0.5-2)**	**<0.001**		
Dyslipidaemia	0.1	(-0.4-1)	0.71		
Statins	**1**	**(0.3-1)**	**0.004**		
Aspirin	0.1	(-0.5-1)	0.71		
Carotid intima-media, microns	0.001	(-0.001-0.003)	0.42		
Carotid plaque	0.3	(-0.2-1)	0.25		
SLE related data					
Disease duration, years	**0.03**	**(0.01-0.1)**	**0.014**	0.02	(-0.002-0.05) 0.065
CRP, mg/dl	0.02	(-0.01-0.04)	0.14	0.01	(-0.004-0.03) 0.12
SLICC-DI	**0.4**	**(0.3-0.5)**	**<0.001**	**0.4**	**(0.2-0.5)** **<0.001**
SLICC-DI 1	**1**	**(0.5-2)**	**<0.001**	**0.9**	**(0.3-1)** **0.002**
SLEDAI	**0.07**	**(0.007-0.1)**	**0.031**	**0.07**	**(0.01-0.1)** **0.022**
SLEDAI categories,					
No activity		ref.			ref.
Mild	-0.3	(-0.9-0.3)	0.30	-0.3	(-0.9-0.3) 0.28
Moderate to very high	0.4	(-0.3-1)	0.27	0.5	(-0.2-1) 0.17
Auto-antibody profile					
Anti-DNA positive	-0.1	(-1-0.5)	0.78		
Anti-ENA positive	1	(-0.0004-1)	0.050	**0.7**	**(0.05-1)** **0.034**
Anti-SSA	-0.04	(-1-1)	0.91		
Anti-SSB	-1	(-3-2)	0.58		
Anti-RNP	0.1	(-1-1)	0.73		
Anti-Sm	-0.9	(-2-0.05)	0.062	-0.8	(-2-0.1) 0.093
Anti-ribosome	-0.3	(-2-1)	0.63		
Anti-nucleosome	0.5	(-0.4-1)	0.29		
Anti-histone	0.2	(-1-1)	0.76		
Antiphospholipid syndrome	**1**	**(0.2-2)**	**0.010**	**1**	**(0.3-2)** **0.004**
Antiphospholipid autoantibodies					
Lupus anticoagulant	-0.2	(-1-1)	0.65		
ACA IgM	0.04	(-1-1)	0.94		
ACA IgG	-0.02	(-1-1)	0.95		
Anti beta2 glycoprotein IgM	-1	(-2-0.3)	0.14	-0.8	(-2-0.3) 0.17
Anti beta2 glycoprotein IgG	0.3	(-1-1)	0.52		
Current prednisone	**1**	**(0.3-1)**	**0.003**	**0.7**	**(0.2-1)** **0.006**
Prednisone, mg/day	0.1	(-0.05-0.2)	0.28		
Hydroxychloroquine	-0.5	(-1-0.07)	0.092	-0.4	(-1-0.2) 0.16
Methotrexate	0.5	(-0.3-1)	0.24		
Mycophenolate mofetil	-0.3	(-1-1)	0.54		
Azathioprine	**0.9**	**(0.2-2)**	**0.009**	**0.9**	**(0.2-2)** **0.010**
Rituximab	-0.4	(-2-1)	0.56		
Belimumab	1	(-0.5-2)	0.19	1	(-0.3-3) 0.10

In this analysis RDW is the dependent variable. Significant *p*-values are shown in bold.
BMI: body mass index; C3 C4: complement; CRP: C-reactive protein; LDL: low-density lipoprotein; ACA: anticardiolipin; ANA: antinuclear antibodies. HDL: high-density lipoprotein; ENA: extractible nuclear antibodies.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. SLEDAI categories were defined as: 0, no activity; 1-5 mild; 6-10 moderate; >10 high activity, >20 very high activity
SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index. Dyslipidaemia was defined if one of the following was present: total cholesterol >200 mg/dl, triglycerides >150 mg/dl, HDL cholesterol <40 in men or <50 mg/dl in women, or LDL cholesterol >130 mg/dl. Significant *p*-values ae given in bold.

Table IV. Systemic lupus erythematosus disease activity index –SLEDAI-2K– relationship of items with RDW values.

	Red Cell Distribution Width, %			
	n	%	beta coef. (95%),	*p*
Seizures	1	0	2 (-2-6)	0.32
Psychosis	1	0	-1 (-5-4)	0.77
Organic brain syndrome	0	0	-	-
Visual disturbance	1	0	1 (-4-5)	0.78
Cranial nerve disorder	1	0	-1 (-5-3)	0.63
Lupus headache	1	0	-1 (-5-3)	0.66
ACVA	0	0	-	-
Vasculitis	1	0	2 (-3-6)	0.45
Arthritis	9	3	-0.3 (-2-1)	0.64
Myositis	0	0	-	-
Urinary cylinders	7	3	**3 (1-4)**	**<0.001**
Haematuria	16	6	**2 (1-3)**	**<0.001**
Proteinuria	5	2	0.2 (-2-2)	0.82
Pyuria	11	4	1 (-0.1-2)	0.063
Rash	21	8	-0.1 (-1-1)	0.90
Alopecia	11	4	-1 (-2-0.3)	0.16
Mucosal ulcers	14	5	**1 (0.2-3)**	**0.022**
Pleurisy	3	1	1 (-2-4)	0.39
Pericarditis	1	0	-1 (-5-4)	0.81
Low complement	76	28	**-1 (-1-(-0.03))**	**0.038**
Elevated anti-DNA	85	31	0.03 (-1-1)	0.92
Fever	2	1	**5 (2-8)**	**<0.001**
Thrombocytopenia	10	4	1 (-1-2)	0.30
Leukopenia	19	7	1 (-0.1-2)	0.071

In this analysis RDW is the dependent variable. Significant *p*-values are depicted in bold. ACVA: Acute cerebrovascular accident, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index-2000, RDW: Red Cell Distribution Width, DNA: deoxyribonucleic acid. Significant *p*-values ae given in bold.

the inactive group with SLE and in the control group with statistically significant differences (18). In our series, the RDW was positively correlated with the SLEDAI score. This was also described in a report of 193 patients and 98 controls in which RDW was correlated with the SLEDAI-2K score (19). This was shown to be the case regardless of anemia status (20, 21). Similarly, increased RDW has been described as a significant predictor of future renal relapse in patients achieving remission. In this regard, in a report of 172 patients with biopsy-proven lupus nephritis, an increase in RDW during follow-up (defined as a greater than 0.5% increase in RDW) was associated with renal flares (22). RDW has also been associated with other SLE features such as fatigue (23), correlates with serum IgM, CRP and ESR, and decreases after glucocorticoids treatment (24), and is associated with higher serum levels of fibrinogen (21). Besides, in a study that assessed RDW to platelet ratio, this ratio positively correlated with SLEDAI and patients with elevated ratio had higher disease activity and more adverse pregnancy outcomes (25). However, all the aforementioned studies recruited a smaller number of patients compared to ours, generally lacked multivariate analysis, and in many cases, the series were not fully characterised. Furthermore, the association between SLICC damage index and RDW has not been previously described in the literature until the present work.

It is noteworthy that in our series, when splitting the SLEDAI-2K score into its individual items, the associations of RDW were basically found with the presence of urinary casts, haematuria, mucosal ulcers, low complement levels and fever. The association between hypocomplementaemia and RDW is of great interest since low complement levels have been associated with disease activity. Since hypocomplementemia was present in one-third of SLE patients, it is possible that alteration of the complement system may be the factor ultimately responsible for the association between RDW and SLEDAI-2K levels.

In our series, the individual elements of the SLICC cumulative damage index, cataract, pulmonary hypertension, angina, venous thrombosis and skin manifestations and diabetes, were those that showed significant associations with RDW (all of them positively). However, all these disease features were small in number. Therefore, it appears that for the cumulative damage of the disease, it is its total count, and not a single manifestation, that drives the relationship between SLICC and RDW.

Additional associations between RDW and some SLE disease characteristics were found in our study. In this sense, in some way the relationship of azathioprine with high levels of RDW can be expected since this drug has been related to haematological alterations such as bone marrow suppression (26). On the other hand, the association between the use of glucocorticoids and RDW is probably a consequence of the fact that this drug is used in patients with greater activity and damage. Similarly, elevations in RDW have been associated with venous thrombosis, including pulmonary embolism (27). This relationship may also exist in patients with SLE given the association found in our series between antiphospholipid syndrome and high RDW values.

Besides, none of the patients was under cyclophosphamide when patients were recruited. But one had previously been with this drug. We cannot ascertain the impact this has had on the patient's blood count. Nevertheless, given that this is the sole patient who has been administered this medication, we estimate that its effect on the results of our study is likely negligible.

Our study may have significant clinical implications. Assessing SLE activity or damage scores in clinical practice is not commonly done due to the lengthy nature of the scores, the multiple aspects they encompass, and the time required for completion. However, given the association between RDW and disease damage and activity scores, we believe that this haematological parameter could potentially serve as a surrogate biomarker for measuring the activity or damage of the disease, albeit approximately. This finding is particularly

Table V. Relationship of Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR Damage Index -DI-) score items to RDW.

	Red Cell Distribution Width, %			
	n	%	beta coef. (95%),	*p*
Ocular				
Any cataract ever	29	11	**1 (0.02-2)**	**0.045**
Retinal change or optic atrophy	33	12	1 (-0.3-1)	0.17
Points ≥1 in the domain	63	22	1 (-0.01-1)	0.082
Neuropsychiatric				
Cognitive impairment	7	3	-1 (-2-1)	0.35
Seizures requiring therapy for 6 months	15	5	-0.2 (-1-1)	0.71
Cerebrovascular accident ever	13	5		
Cranial or peripheral neuropathy	5	2	0.3 (-2-3)	0.83
Transverse myelitis	1	0	1 (-4-5)	0.80
Points ≥1 in the domain	40	14	0.3 (-0.4-1)	0.90
Renal				
Estimated or measured glomerular filtration rate <50%	13	5	0.1 (-1-1)	0.88
Proteinuria 3.5 gm/24 hours	7	3	0.3 (-1-2)	0.67
End-stage renal disease	4	1	-0.05 (-1-1)	0.90
Points ≥1 in the domain	28	10	0.02 (-1-1)	0.66
Pulmonary				
Pulmonary hypertension	4	1	**4 (1-6)**	**0.002**
Pulmonary fibrosis	4	1	1 (-1-3)	0.25
Shrinking lung	2	1	-2 (-5-0.4)	0.095
Pleural fibrosis	1	0	-2 (-6-2)	0.26
Pulmonary infarction	1	0	-2 (-6-3)	0.46
Points ≥1 in the domain	19	7	0.4 (-1-1)	0.12
Cardiovascular				
Angina or coronary artery bypass	4	1	**5 (3-7)**	**<0.001**
Myocardial infarction ever	2	1	1 (-2-4)	0.35
Cardiomyopathy	2	1	1 (-4-5)	0.76
Valvular disease	9	3	1 (-1-3)	0.18
Pericarditis for 6 months, or pericardiectomy	2	1	2 (-1-5)	0.20
Points ≥1 in the domain	23	8	2 (1-3)	0.57
Peripheral vascular				
Claudication for 6 months	3	1	-0.5 (-3-2)	0.70
Minor tissue loss (pulp space)	5	2	1 (-1-3)	0.19
Significant tissue loss ever	0	0	-	-
Venous thrombosis	14	5	**1 (0.3-3)**	**0.016**
Points ≥1 in the domain	34	12	1 (0.5-2)	0.34
Gastrointestinal				
Infarction or resection of bowel	22	8	**2 (1-2)**	**0.001**
Mesenteric insufficiency	1	0	4 (-0.2-8)	0.061
Infarction or resection of bowel below duodenum, spleen, liver, or chronic peritonitis	1	0	-0.5 (-5-4)	0.82
Stricture or upper gastrointestinal tract surgery ever	0	0	-	-
Pancreatic insufficiency	0	0	-	-
Points ≥1 in the domain	28	10	1 (0.3-2)	0.877
Musculoskeletal				
Muscle atrophy or weakness	3	1	1 (-2-3)	0.56
Deforming or erosive arthritis	40	15	0.5 (-0.2-1)	0.19
Osteoporosis with fracture or vertebral collapse	23	9	1 (-0.3-1)	0.22
Avascular necrosis	7	3	-0.2 (-2-1)	0.81
Osteomyelitis	1	0	1 (-3-5)	0.72
Tendon rupture	4	2	0.3 (-2-2)	0.80
Points ≥1 in the domain	89	31	1 (0.1-1)	0.43
Skin				
Scarring chronic alopecia	16	6	-0.3 (-1-1)	0.60
Extensive scarring or panniculum	10	4	1 (-1-2)	0.25
Skin ulceration	4	1	1 (-1-3)	0.49
Points ≥1 in the domain	39	14	**1 (-0.1-1)**	**0.037**
Premature gonadal failure	19	7	0.2 (-1-1)	0.73
Diabetes (regardless of treatment)	18	6	**1 (0.03-2)**	**0.044**
Malignancy (exclude dysplasia)	11	4	1 (-0.1-3)	0.070

SLICC: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. In this analysis RDW is the dependent variable. Significant *p*-values ae given in bold.

noteworthy as its relationship with the scores was found to be independent of covariates.

In conclusion, RDW is an inexpensive and easily accessible measure of the change in circulating erythrocyte volume calculated by most automated blood cell counters as part of routine blood cell count analysis. RDW was associated with disease activity and damage in SLE patients in our large cohort of SLE patients after adjustment for confounders. Therefore, we propose that RDW can be considered as a surrogate biomarker of disease activity and damage in SLE.

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