



Research Article

Association between Red Cell Distribution Width to Platelet Ratio and Disease Activity among Iraqi Patients with Systemic Lupus Erythematosus

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Abstract

Background: The link between red blood cell distribution width-to-platelet ratio (RPR) and disease activity in systemic lupus erythematosus (SLE) is not well understood. **Aim:** To investigate the association between RPR levels and disease activity in SLE. **Methods:** This was a case-control study conducted at Baghdad Teaching Hospital, Medical City from July 2020 to March 2021. Seventy SLE patients were compared with 70 healthy controls. The diagnosis was made using the American College of Rheumatology SLE criteria. **Results:** SLE patients had a mean age of 35.2 ± 12.03 years, while controls had a mean age of 36.3 ± 9.9 years ($P=0.5$). Females represent 97.1% of SLE patients and 88.6% of controls. The average disease duration was 4.98 ± 0.05 years. The disease activity index (SLEDAI) was 16.4 ± 4.8 . SLE patients had a lower platelet count than controls, and the median (IQR) of RDW was larger than that of controls. SLE patients had a greater median (IQR) of RPR than controls (0.058 ; $0.04-0.07$ vs. 0.045 ; $0.039-0.053$). The RPR and SLEDAI showed strong positive association. The optimal cutoff point for distinguishing SLE patients from controls was 0.0455 , with 79% sensitivity and 51% specificity. The RPR was not significantly affected by sociodemographic or clinical factors. **Conclusion:** The RPR was positively correlated with disease activity in SLE patients, and may be a valid measure to differentiate between SLE patients and healthy controls. Sociodemographic and other clinical characteristics do not significantly affect RPR.

Keywords: SLE, Red cell distribution width, Platelets count, Disease activity

الارتباط بين عرض توزيع الخلايا الحمراء إلى نسبة الصفائح الدموية ونشاط المرض لدى المرضى العراقيين المصابين بالذئبة الحمامية الجهازية

الخلاصة

الخلفية: الصلة بين نسبة عرض الصفائح الدموية لتوزيع خلايا الدم الحمراء (RPR) ونشاط المرض في الذئبة الحمامية الجهازية (SLE) غير مفهومة جيدا. **الهدف:** التحقيق في العلاقة بين مستويات RPR ونشاط مرض SLE. **الطرائق:** هذه دراسة على مدى SLE أجريت في مستشفى بغداد التعليمي، المدينة الطبية من يوليو 2020 إلى مارس 2021. تمت مقارنة سبعين مريضا مع 70 من الأصحاء. تم التشخيص باستخدام معايير الكلية الأمريكية لأمراض الروماتيزم. **النتائج:** كان متوسط عمر المرضى 35.2 ± 12.03 سنة، في حين كان متوسط عمر الأصحاء 36.3 ± 9.9 سنة ($P=0.05$). وتمثل الإناث 97.1% من مرضى ال SLE و 88.6% من الأصحاء. ومتوسط مدة المرض 4.98 ± 0.05 سنة. وكان مؤشر نشاط المرض 16.4 ± 4.8 . كان عدد الصفائح الدموية لمرضى SLE أقل من الأصحاء، وكان متوسط (IQR) من RDW أكبر من الأصحاء. كان لدى مرضى SLE متوسط (IQR) أكبر من RPR للأصحاء (0.058 ; $0.04-0.07$ مقابل 0.045 ; $0.039-0.053$). وأظهر كل من RPR و SLEDAI ارتباطا إيجابيا قويا. كانت نقطة القطع المثلى لتمييز مرضى SLE عن الضوابط هي 0.0455 ، مع حساسية 79% و 51% خصوصية. ولم يتأثر تقرير أداء البرنامج بشكل كبير بالعوامل الاجتماعية الديموغرافية أو السريرية. **الاستنتاج:** ارتبط RPR بشكل إيجابي بنشاط المرض لدى مرضى SLE، وقد يكون مقياسا صالحا للتمييز بين مرضى SLE والأصحاء. الخصائص الاجتماعية الديموغرافية وغيرها من الخصائص السريرية لا تؤثر بشكل كبير على RPR.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is the quintessential systemic autoimmune illness and one of the most diverse disorders addressed by doctors. This heterogeneity makes diagnosis, treatment, and prognosis extremely difficult. Despite these obstacles, SLE mortality has decreased from 50% in the pre-corticosteroid era to a survival rate of 95% for 15 years in the modern era [1,2]. Globally, SLE rates ranged from 0.3-23.7 per 100,000 persons per year, with a frequency of 6.5 to 178.0 per 100,000 people per year [3,4]. SLE was substantially more common in women than in men, with a ratio of 9:1-15:1 [5], and it was 10.6:1 in Iraq, according to Al-Derzi *et al.* (2020) [6]. The peak age of prevalence for females was 45-69 years, and for males it was 40-89 years [7]. Genetic causes, hormonal imbalances, and environmental factors all have a part in the development of SLE. The most prominent environmental factors involved in SLE pathogenesis include ultraviolet (UV) light and different illnesses [8]. Many researchers have reported the association of RDW with DAS-28, a widely used disease activity tool for rheumatoid arthritis (RA). An increased rate of RDW, as well as RDW changes in the first year after diagnosis, has been found to be associated with a high risk of cardiovascular accidents (heart failure, ischemic heart disease, or cerebrovascular accidents), and the significant correlation remained after adjusting for gender and age [9]. Previous studies proved that RDW was associated with the increased severity of inflammatory bowel disease (IBD), RA [10], and psoriatic arthritis [11]. Another recent study has also concluded that RDW was increased in patients with SLE [12,13]. Due to the effect of inflammatory cytokines, there is a release of premature erythrocytes into the circulation and a resultant increase in RBC distribution width [14]. Moreover, platelets play a major role in SLE pathogenesis and represent a great potential for novel biomarkers and drug development [15]. Accordingly, the ratio of RDW to total platelet count, known as RPR, can be evaluated as a prognostic index to determine the degree of severity of systemic inflammatory response syndrome and hence the outcome of SLE. The present study aims to investigate the association between RDW to platelet ratio (RPR) levels and disease activity in SLE patients.

METHODS

Study design

From July 2020 to the end of March 2021, a case-control research was undertaken at the Rheumatology Unit of Baghdad Teaching Hospital in Medical City.

Sample selection

This study included 70 Iraqi patients with SLE who attended the Unit of Rheumatology at Baghdad Teaching Hospital, as well as 70 healthy volunteers who served as controls. The American College of Rheumatology (ACR) criteria for systemic lupus erythematosus were used to make the diagnosis. Each participant gave their informed

consent in accordance with the Helsinki Declaration of 1998 and its updates. Based on the administrative order for authorizing the study plan for the rheumatology and medical rehabilitation diploma, the Ethics Committee of the Department of Medicine, College of Medicine, University of Baghdad, granted ethical permission (ID: 802 in 21st October 2020). Patients were excluded from the study if they were clinically suspected of having RA but did not meet the inclusion criteria, if they had other autoimmune illnesses including RA, IBDs, or psoriasis, if they had other skin diseases or allergies, or if they had inflammatory or infectious diseases. They are also ruled out if they have other chronic conditions like cardiovascular, hematological, liver, renal, or malignant disorders, diabetes, or hypertension, or if they have had a blood transfusion in the last four months. Women who were pregnant or had given birth within the previous six months were also excluded from the study.

Data collection and entry

Data from patients and controls was collected through interviews and questionnaires and entered into a specifically developed form. The surveys were divided into two sections: the first contained general demographic information such as age, gender, smoking status, drugs used, height, and weight. Body mass index (BMI) was calculated using the formula $BMI (kg/m^2) = \text{weight}/\text{height}^2$. Since the onset of symptoms and diagnosis by the physician, the duration of SLE was tracked. All controls were evaluated for their age, sex, smoking status, height, and weight.

Evaluation and analysis methods

Hemoglobin (Hb), ESR, red cell distribution width (RDW), and mean platelet volume were measured in blood samples from both groups (MPV). WBC count, neutrophil count, lymphocyte count, monocyte count, platelet count, ESR, and CRP were all measured. After receiving the laboratory findings, the platelet-lymphocyte ratio for each participant was manually determined by dividing the platelet count by the lymphocyte count. Similarly, by dividing the lymphocyte count by the monocyte count, the blood lymphocyte/monocyte ratio was computed manually. The SLE Disease Current Activity Form (SLEDI) was used to assess disease activity, which is a simple and logical tool for describing and assessing diverse signs of active SLE and thereby assessing the efficacy of medication in controlling the disease [16].

Statistical analysis

Microsoft Excel and the statistical program for social sciences (SPSS) version 23 were used for data entry and analysis. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to see if the data had a normal distribution. For normally distributed values, the mean and standard deviation were utilized, whereas for non-normally distributed variables, the median and interquartile range were used. The qualitative data is represented using

frequency and percentages. The data is presented using box plot charts and bar charts. The association between RPR and the patient's general and clinical features was investigated using multiple linear regression. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check for normal distribution in standardized residuals in order to rule out any interactions. Statistical significance was defined as a *P* value of less than 0.05.

RESULTS

The average age of SLE patients was 35.2±12.03 years, compared to 36.3±9.9 years for controls; however, this difference was not statistically significant. Females account for 97.1% of SLE patients and 88.6% of the control group, respectively; whereas men account for 2.9% and 11.4%, respectively. As seen in Table 1, this relationship was statistically significant. Primary education was the most common among SLE patients (40.6%), while college and postgraduate degrees were represented by 20% and 20% of controls, respectively (Table 1).

Table 1: Demographic characteristics of the SLE patients and controls

Variables	SLE Patients (n=70)	Controls (n=70)	P-value
Age (year)	35.2±12.03	36.3±9.9	0.5
Gender			
Females n (%)	68(97.1)	62(88.6)	0.049
Males n(%)	2(2.9)	8(11.4)	
BMI (kg/m ²)	26.8±5.2	26.8±3.9	0.9
Smokers +ve n(%)	2(2.9)	4(5.7)	0.34
Education			
Illiterate	2(2.9)	4(5.7)	0.02
primary school	28(40.6)	12(17.1)	
Secondary school	20(29)	26(37.1)	
College	17(24.6)	14(20)	
Postgraduate	2(2.9)	14(20)	

All patients had an active disease with a mean disease duration of 4.98±0.05 years, and 16.4±4.8 was the SLEDAI. Steroids and HCQ were the most widely utilized medicines, with 90% and 90%, respectively, followed by AZT (31.4%) and MTX (12.9%). In 45.7% of the patients, the ANA marker was positive, whereas in 51.4% of the patients, the anti-ds-DNA marker was positive. C3 and C4 concentrations were 70.5±62.2 mg/dl and 15.5±12.9 mg/dl, respectively. Proteinuria was discovered in 35.9% of the patients (Table 2).

Table 2: Clinical characteristics, medications used, and laboratory investigations in SLE patients

Variables	Value
Disease duration (year)	4.98±0.05
Disease activity n(%)	
Active	70(100)
Inactive	0(0)
SLEDAI (mean±SD)	16.4±4.8
Medications n(%)	
NSAIDs	7(10)
Steroids	63(90)
HCQ	63(90)
MTX	9(12.9)
AZT	22(31.4)
SSZ	3(4.3)
MMF	6(8.6)
Cyclophosphamide	7(10)
Rituximab	6(8.6)
ANA n(%)	
Positive	32(45.7)
Negative	13(18.6)
Not done	25(35.7)
Anti-ds-DNA	
Positive	36(51.4)
Negative	8(11.4%)
Not done	26(37.1%)
C3 (mg/dL)	70.5±62.2
C4 (mg/dL)	15.5±12.9
Proteinuria present	23(35.9)

SLEDAI, systemic lupus erythematosus disease activity index; HCQ, hydroxychloroquine; AZT, azathioprine; SSZ, sulfasalazine; MMF, mycophenolate mofetil; ANA, antinuclear antibody; C3 complement 3, C4, complement 4; Anti-ds-DNA, anti-double stranded deoxyribonucleic acid.

SLE patients had a substantially lower mean platelet count (242.2±86.4) than controls (278.8±63.4) (*P*<0.05). SLE patients had a significantly higher RDW value (14.2±3.4) than controls (12.55±1.47) (*P*<0.05). SLE patients had a substantially greater median (IQR) red cell distribution width to platelet ratio (RPR) (0.058; 0.04-0.074) than controls (0.045; 0.039-0.053) (*P*<0.05). (Table 3 and Figure 1). There was a significant positive correlation between RPR and SLEDAI score (*r*=0.359, *P*<0.05) (Figure 2).

Table 3: Platelet count, red cell distribution width, and RPR in patients and controls

Variables	SLE Patients	Controls	P-value
Platelets count (10 ³ /μl)	242.2±86.4	278.8±63.4	0.005
RDW (%)	14.2±3.4	12.55±1.47	0.0001
RPR (Ratio)	0.058	0.045	0.0001
Platelet volume	7.8±1.2	8.1±0.9	0.22

Values are presented as mean±SD, percentage and ratio. RDW, red cell distribution width; RPR, red blood cell distribution width to platelet ratio

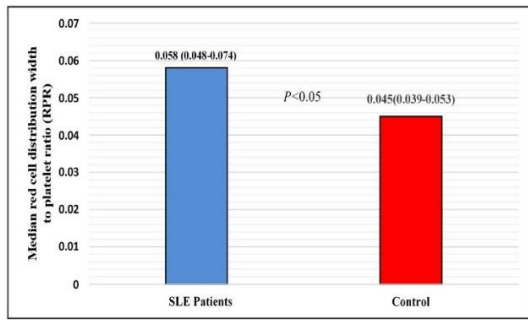


Figure 1: The median (IQR) of red blood cell distribution width to platelet ratio (RPR) among SLE patient and controls. [SLE: systemic lupus erythematosus; RPR: Red blood cell distribution width to platelet ratio; IQR: interquartile range].

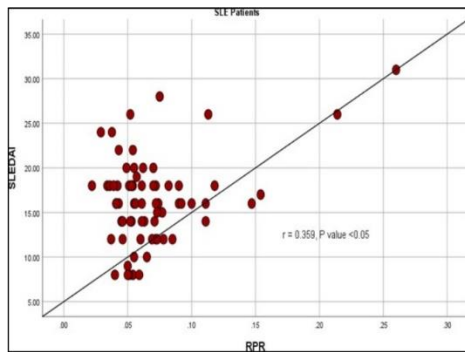


Figure 2: The scatter plot diagram for the correlation of SLEDAI and RPR among SLE patients.

Multi variate linear regression analysis of the RPR with different patients’ characteristics shows positive association with SLEDAI ($\beta=0.697$, $P<0.05$) (Table 4). The Receiver operator curve was done to identify the cutoff point of sensitivity and specificity for SLE diagnosis. Figure 3 and Table 5 demonstrated a significant area under the curve (AUC=0.755; 95% CI=0.675-0.835) ($P= 0.001$). The optimum cut off point of RPR was 0.0455, and the analysis of data showed that this cut off point had 79% sensitivity, 51% specificity 51%, 65% accuracy, 62% PPV 62%, and 70.6% NP (Table 6).

Table 4: Multiple linear regression analysis to find the correlation between demographic and clinical characteristics with RPR

Variables	β	P-value
Age	0.304	0.413
Females vs. males	-0.592	0.187
BMI	0.045	0.887
Disease duration	-0.394	0.363
SLEDAI	0.697	0.045
<i>Medications</i>		
NSAIDs	-0.36	0.31
Steroids	0.104	0.73
SSZ	-0.156	0.595
AZT	0.074	0.826
MMF	-0.013	0.972
Cyclophosphamide	-0.362	0.336
Rituximab	-0.182	0.617
ANA	0.54	0.283
Anti-ds-DNA	-0.484	0.241
C3 mg/dL	-0.629	0.187
C4 mg/dL	0.693	0.227
Proteinuria vs. non-proteinuria	-0.129	0.736

β : Regression coefficient; SLEDAI: systemic lupus erythematosus disease activity index; BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs; SSZ: Sulfasalazine; AZT: Azathioprine; MMF: Mycophenolate mofetil; ANA: Antinuclear antibody; Anti-ds-DNA: Anti-double stranded deoxyribonucleic acid.

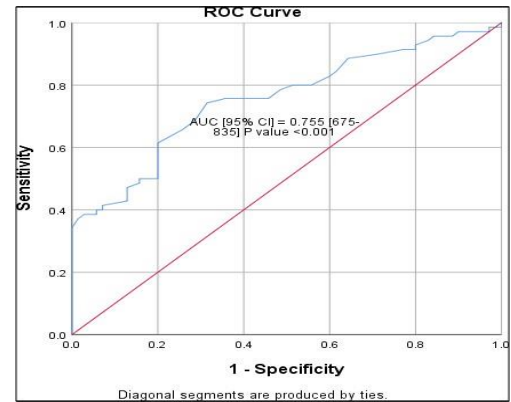


Figure 3: Validity of Receiver operator curve (ROC) test for RPR to differentiate between SLE patients and controls

Table 5: Validity parameters of ROC of RPR

Variable	AUC	Std. Error	95% CI	P-value
RPR	0.755	0.041	0.675-0.835	<0.001

RPR, Red blood cell distribution width to platelet ratio; AUC, area under the curve; CI, confidence interval

Table 6: The optimum cut off value sensitivity, specificity, accuracy, PPV and NPV

RPR cut-off point	Sensitivity	Specificity	False positive	False negative	Accuracy	PPV	NPV
≥ 0.0455	79%	51%	49%	21%	63%	62%	70.6%

RPR, Red blood cell distribution width to platelet ratio; PPV, positive predictive value; NPV, negative predictive value

DISCUSSION

To the best of our knowledge, the association between RPR value and SLE disease activity has not been elucidated. The aim of this study is to see if RPR can be used to predict

SLE disease activity and severity in SLE patients, as well as to see if it has any relationships with other inflammatory markers in SLE patients. Because SLE is a complicated chronic autoimmune inflammatory illness that affects many different body organs [17]. The assessment of SLE

disease activity is critical for evaluating products, changes in SLE patient groups, proposed reactions to a new treatment, and the disorder itself. Anisocytosis (differences in RBC volume) is measured by RDW [18], and RPR was developed as a unique and quick laboratory assessment for predicting mortality in a variety of illnesses [19]. When compared to liver biopsy, Xie and Chen [20] found RPR to be a noninvasive and cost-effective predictor of fibrosis and cirrhosis in chronic hepatitis B. Similarly, Narayanan *et al.* used the RPR value to estimate the severity of acute pancreatitis and enhance survival [21]. The average age of SLE patients was 35.2 years, with females accounting for 97.1 percent of SLE patients and a mean disease duration of 4.98 years, according to the current study. Xie *et al.* [20] described the first two values as being higher. Mohamed *et al.* found similar results, with a mean age of 34.53 years, female forms in 86.6 percent of patients, and a mean disease duration of 4.085 years [13]. In this regard, Ibrahim *et al.* discovered that SLE patients ranged in age from 16 to 45, that 80% of them were females, and that the disease duration was 3.63 years [22]. The majority of SLE patients had only received primary education, and the average BMI was 26.8 years old, according to the current study. Abd-Alrasool *et al.* found a mean age of 33.6 years, with the majority of the patients being females, and an illness duration of 2-9 years [23]. Gorial *et al.* reported a mean age of 31.75 years and a mean disease duration of 19.62 months in this study. Positive smokers made up 2.9 percent of SLE patients in the current investigation, which was similar to previous results [24], and no significant variations in BMI values were seen when compared to healthy people [25]. All of the subjects in this study had active disease, and the SLEDI value was 16.4, which was lower than the value reported by other researchers [24]. The majority of patients were treated with steroids and HCQ, with varying values for the other medicines, according to the current study, which was consistent with a previous report. Furthermore, the SLEDI value given was found to be lower than that of Gorial *et al.*, indicating a reduced rate of active disease status [24]. In terms of proteinuria, the recent study found that 35.9% of SLE patients are proteinuric. According to Chedid *et al.*, 60% of patients exhibited isolated low-level proteinuria coupled with acute renal damage and hematuria. This can be explained by the fact that 76% of patients had histological evidence of lupus nephritis [26]. In this investigation, the mean platelet count in SLE patients was considerably lower than in controls. Patients with active SLE had lower MPV than those with inactive SLE, according to Hartmann *et al.* [27]. They also discovered a weak negative link between the SLEDAI and the MPV, as well as no correlation between MPV and CRP, ESR, C3 and C4. The RDW value in SLE patients was substantially greater than in controls, according to the current study. Shoeib *et al.* observed similar findings, indicating that lupus patients with high disease activity have a significantly larger rise in RDW [28]. RDW was linked to inflammation and anemia, according to Vayá *et al.* [12] and Lee *et al.* [29]. Meanwhile, Nada [30] discovered a link between RDW and chronic inflammation and oxidative stress. Lippi *et al.* [31] confirmed similar

findings showing the substantial relationship between RDW and ESR.

Conclusion

In SLE patients, the RBC distribution width-to-platelet ratio (RPR) was found to be substantially linked with disease activity. With fair accuracy, the RPR was a valid metric for distinguishing between SLE patients and healthy controls. The effects of sociodemographic and other clinical variables on RPR were not significant.

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Conflicting interests

Nothing declared.

Data sharing statement

Data will be available based on a reasonable request to the corresponding author.

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