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Original article

The Clinical Significance of Hematological Parameters as a Marker of Disease Activity in Juvenile Systemic Lupus Erythematosus

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Abstract:

Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that impacts the body's connective tissues and is characterized by a propensity to flare up. This study intended to demonstrate the predictive power of hematological markers for determining the disease activity of Juvenile systemic lupus erythematosus (jSLE). **Patients and Methods:** The study involved 50 jSLE children and 50 apparently healthy controls. All children were exposed to clinical examinations, and a complete blood count was performed. Hematological parameters, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and red cell distribution width/platelet ratio (RPR), were directly calculated from the measured values. The organ function tests and immunological markers were collected from patients' files. Disease activity was assessed serologically and by the SLE Disease Activity Index 2000 (SLEDAI-2k). **Results:** Hematological parameters NLR, PLR and RPR were considerably raised among jSLE patients than controls, and in patients with active than inactive disease. Also, NLR, PLR and RPR were correlated with disease activity assessed serologically and by the SLEDAI-2k. In the multivariate analysis, higher lymphocyte levels were identified as a negative predictor of disease activity (odds ratio (OR)=0.776), and the increased NLR, PLR and RPR were identified as positive predictors of disease activity (OR=1.8, 1.78 and 1.96, respectively). **Conclusion:** NLR, PLR, and RPR can serve as simple, inexpensive and readily available biomarkers for indicating jSLE disease activity.

Keywords: Hematological parameters; Disease activity; jSLE; NLR; PLR

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that impacts the body's connective tissues and is characterized by a propensity to flare up. [1] It is a multisystem disease that could impact various systems, including musculoskeletal, hematological, renal, neurological, and cardiovascular systems, with variable severities of clinical manifestations. [2]

The clinical manifestations of SLE are affected by the age at which it first appears. [3] The term juvenile systemic lupus erythematosus (jSLE) refers to SLE that manifests before the age of eighteen years. Compared to adult SLE, adverse clinical characteristics were more prevalent in jSLE, e.g. malar rash, hematologic and renal involvements, in addition to increased disease activity and a strong correlation with anti-dsDNA antibodies. [4]

Evaluating the disease activity in SLE patients has always been challenging. Acute phase reactants are not typically elevated in cases of SLE [5], and other parameters of inflammation such as leukocytosis, thrombocytosis, low albumin, and low complement values are usually influenced by the illness itself rather than being a sensitive indicator of disease activity. [6] Composite scores, including the SLE Disease Activity Index 2000 (SLEDAI-2K), are applied for evaluating the SLE activity. However, it is not particularly possible to rely on these indexes consistently. Therefore, finding simple laboratory markers that may be obtained at practically any medical facility to evaluate the SLE activity is a significant issue that requires attention. [7]

The complete blood count parameters are helpful in assessing disease activity in a range of autoimmune illnesses has drawn more attention in recent years. It has been shown that the values of neutrophils, lymphocytes, and platelets vary during the course of many diseases, indicating their role in systemic inflammation. [8] Therefore, several hematological parameters, including neutrophil/lymphocyte ratios (NLR), platelet/lymphocyte ratios (PLR), and red cell distribution width/platelet ratio (RPR) have been employed as prognostic indicators and effective indicators of inflammation in autoimmune and inflammatory diseases. [9-11]

The role of hematological parameters has been assessed in various disorders, being a simple test that is widely available at a low cost; however, limited data on their value in jSLE are available. [12-15, 10]

Herein, we intended to assess the value of hematological parameters in jSLE patients in comparison to healthy controls, to find the association between hematological scores and disease activity; and to assess their predictive ability of disease activity by logistic regression analysis.

Materials and methods

This case control study based on fifty children younger than eighteen years old diagnosed with jSLE, who were enrolled from the Pediatric Rheumatology outpatient clinic at Benha University Hospitals from September 2023 to August 2024. Diagnosis of jSLE was based on the American College of Rheumatology (ACR) criteria [16], and the Systemic Lupus International Collaborating Clinics (SLICC) criteria. [17] A matching group of fifty healthy children was recruited from the community as controls.

Patients with another autoimmune disease in addition to SLE, other unrelated medical conditions, chronic hematological diseases, malignancy, or acute/chronic infections were excluded.

Data collection

Full history was taken from all children, including the history of disease, related complications, and treatment given. Clinical examination was conducted to evaluate organ affection. The SLE disease activity was measured by SLEDAI-2K, [18] considering inactive disease when SLEDAI≤4. [19]

The SLICC/ACR Damage Index (SDI), [20] was used to measure the organ damage, defining the lack of organ damage when SDI = 0. [21]

Laboratory assessments

A complete blood count was performed using the Sysmex-XN automated blood cell analyzer (Sysmex, Kobe, Japan). Hematological parameters were calculated from complete blood count parameters, as NLR, PLR, and RPR. Other laboratory tests to assess disease activity were performed including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) by immunofluorescence, anti-dsDNA antibodies by enzyme-linked immunosorbent assay, and complement (C3 and C4), in addition to serum creatinine, urea, aspartate transaminase (AST) and alanine transaminase (ALT).

Serological activity was defined as positive anti-dsDNA antibody and/or hypocomplementemia, whilst hypocomplementemia was defined as C3 and/or C4 fractions falling less than lab reference range. [13]

Ethical considerations

The whole study design was accepted by the local ethics committee, Faculty of Medicine, Benha University (MoHP no: 0018122017 / Certificate no: 1017), study no: MS 21-9-2023. After explaining the value of the study and the procedures that would be commenced, informed written consent was attained from the parent/guardian of every participant.

Statistical Analysis

The data were analyzed using SPSS program (version 26.0). The Shapiro test was employed to detect the normality of data distribution. Numerical data were presented as mean (± SD) if (parametric), or median (range) if (non-parametric). The student t-test was applied to compare between two means, or one-way ANOVA if (> two means).

The qualitative data were presented as number (percentage) and tested by chi-square test (if the predictable count is <5 in more than 20% of cells, Fisher's exact test was applied). The receiver operating characteristic (ROC) curve provides a useful way to assess the sensitivity and specificity for quantitative diagnostic measures. Pearson (parametric), or Spearman (Non parametric) correlations were applied to correlate continuous data. Logistic regression analysis was applied to predict risk factors, using generalized linear models. An odds ratio (OR) is a measure of the association between an exposure and an outcome. Probability was considered significant if <0.05.

Results

Demographic data of all included subjects and disease-related data of jSLE patients

This study included fifty jSLE patients and fifty matching controls, age ranged from 7-18 years in both groups. Females comprised the major portion in the two groups, constituting 78% and 76%, respectively. Family history of jSLE had existed in 20% of patients, in contrast to 6% of control, p=0.037. Growth parameters were significantly lower in jSLE than controls (p<0.001) **(table 1).**

In the jSLE group, the mean disease onset age was 10.2±2.9 years (range 6-14 years), the mean disease duration was 3.2±0.9 years (range 1-4 years). The most common clinical characteristic was skin manifestation (84%), followed by fever (62%). During the course of illness, 66% of patients developed skin manifestations, followed by hematological manifestations (60%), renal manifestations (48%), arthritis (42%), neurological manifestations (8%), and serositis (4%).

Immunosuppressive treatment was given to all patients in the form of steroids at a mean duration of 2.9±0.7 years (range 1-4 years); additional treatment was given as hydroxychloroquine, cyclophosphamide, and azathioprine in 22%, 14%, and 10% of patients, respectively.

Laboratory data of jSLE activity are demonstrated in **table 2**. Serological activity was evident in 36 (70%) patients, and disease activity by SLEDAI-2k was documented in 22 (44%) patients. SDI was >0 in 12 (24%) patients.

Laboratory assessment data of the study groups

Patients of the jSLE group had significantly lower hemoglobin and related red blood cell indices. Total leucocytic count (TLC) was insignificantly different between the study groups, but neutrophil

count was considerably raised, and lymphocyte count was reduced in the patient group. Platelet count was significantly lower and other hematological parameters (red cell distribution width (RDW), NLR, PLR, and RPR) were significantly higher among patients **(figure 1).** Other laboratory parameters such as ALT, AST, urea, serum creatinine, CRP and ESR were considerably elevated in the patients than controls **(table 3).**

These hematological parameters did not differ considerably in relation to the immunosuppressive treatment given ($p>0.05$). At the same time, they had a significant negative correlation with hemoglobin level and lymphocyte count, and a significant positive correlation with disease duration, CRP and ESR, and only NLR, PLR, and RPR had significant positive correlations with SLEDAI-2k and SDI score **(table 4).**

Table 1. Demographic data of the studied groups.

Parameter		jSLE group N=50	%	Control group N=50	%	p-value
Age (years)	**Mean±SD**	13.1±3.2		12.8±3.1		0.53
	Range	7-18		7-18		
Gender	**Male**	11	22%	12	24%	0.84
	Female	39	78%	38	76%	
Consanguinity	**Positive**	29	58%	28	56%	0.83
	Negative	21	42%	22	44%	
Family history of SLE	**No**	40	80%	47	94%	0.037*
	Yes	10	20%	3	6%	
Weight percentile	**Mean±SD**	21.3±16.2		53.5±22.1		<0.001*
	Range	3rd-75th		10th -75th		
Height percentile	**Mean±SD**	38.2±23.4		57.2±21.5		<0.001*
	Range	3rd-75th		25th -75th		
BMI percentile	**Mean±SD**	22.4±17.8		45.9±23.4		<0.001*
	Range	3rd-75th		25th -75th		

jSLE: Juvenile systemic lupus erythematosus; SLE: Systemic lupus erythematosus; BMI: Body mass index; SD: Standard deviation.

Table 2. Laboratory results and activity scores of the jSLE patients

Parameter		jSLE group N=50	%
C3 (g/L)	**Mean±SD, range**	0.81±0.23, 0.45-1.25	
	Decreased (Normal 0.75 -1.75 g/L)	29	78%
C4 (g/L)	**Mean±SD, range**	0.08±0.05, 0.04-0.21	
	Decreased (Normal 0.16 – 0.48 g/L)	34	68%
ANA	**Positive**	50	100%
Anti-dsDNA	**Positive**	26	52%
Serological activity	**Serologically inactive**	15	30%
	Serologically active	36	70%
SLEDAI-2k	**Mean±SD, range**	8.5±4.9, 0-18	
	Active	22	44%
SDI score	**Mean±SD, range**	0.69±0.34, 0-3	
	>0	12	24%

jSLE: Juvenile systemic lupus erythematosus; C3: Complement 3; C4: Complement 4; ANA: Anti-nuclear antibody; Anti-dsDNA: Anti double stranded DNA antibody; SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000; SDI score: The SLICC/ACR Damage Index; SD: Standard deviation.

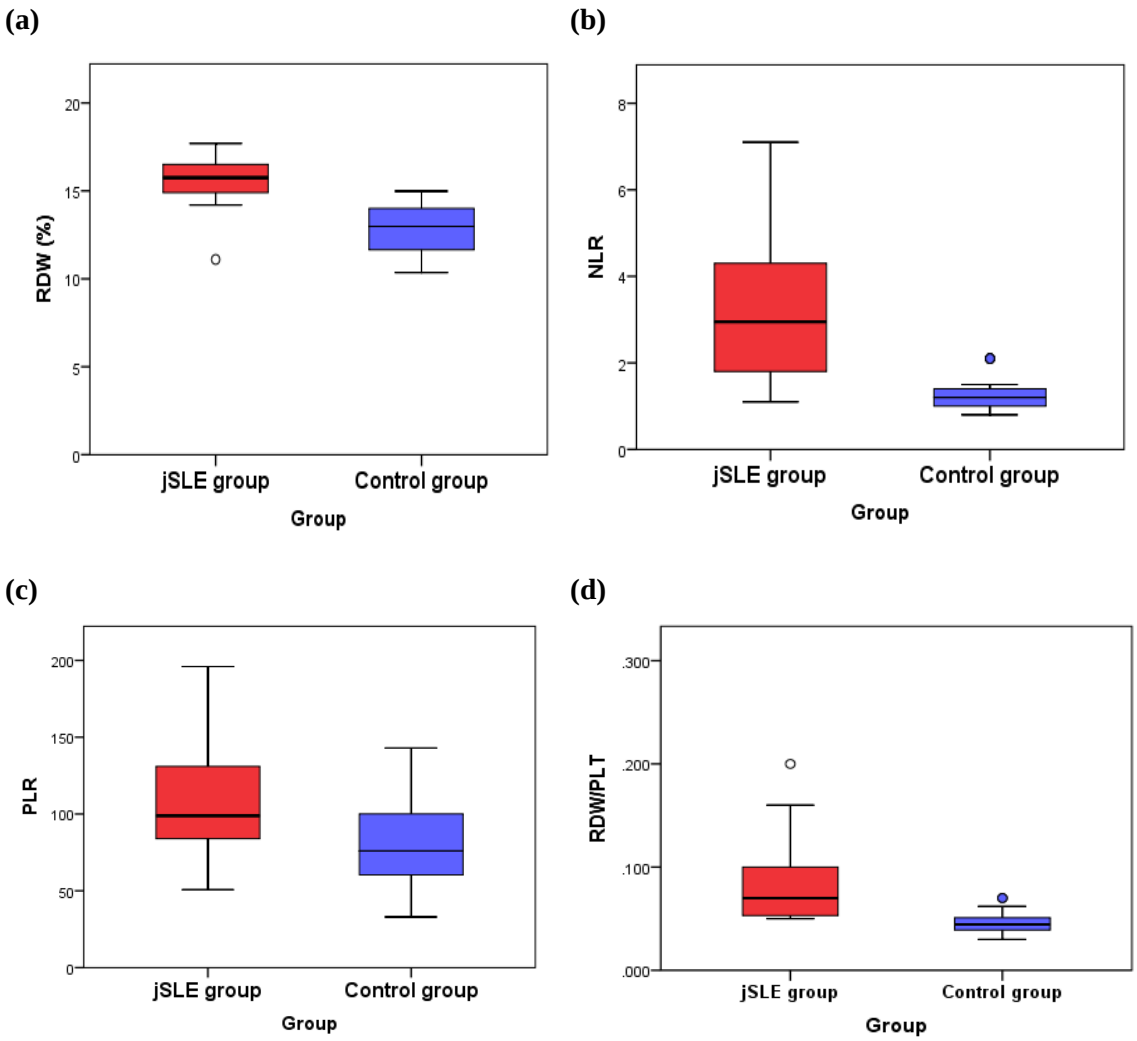

Figure 1: (a) RDW (b) NLR (c) PLR (d) RPR in the studied groups

Assessment of disease activity by hematological parameters

Active state patients either by SLEDAI-2k or serologically had considerably raised NLR, PLR and RPR than patients with inactive state. While there was no statistical difference between groups concerning RDW (**table 5, figures 2).**

The diagnostic performance of hematological parameters to detect disease activity was evaluated; regarding NLR; the area under the curve (AUC) was highest at 0.850 (95% confidence interval (95% CI): 0.743-0.957), p<0.001. and at a cutoff point > 2.9, NLR had the highest sensitivity, and specificity of 86.4% and 89.6%, respectively. Regarding PLR; AUC was 0.729 (95% CI: 0.586-0.871), p=0.006, and at a cutoff point > 125, the sensitivity was modest at 68.1% and the specificity was high at 83.1%.

Regarding RPR; AUC was 0.636 (95% CI: 0.476-0.795), p=0.013, and at a cutoff point > 0.06, the sensitivity and specificity were accepted at 63.6% and 56.3%, respectively. RDW had a non-significant AUC of 0.516, p=0.845 **(table 6, figure 3).**

Using logistic regression analysis to define predictors of disease activity, higher hemoglobin and lymphocyte levels were associated with significantly decreased odds of disease activity (0.711 and 0.776, respectively) in univariate analysis, and

lymphocyte count remained significant in multivariate analysis.

On the other hand, increased ESR, NLR, PLR and RPR were associated with significantly increased odds of disease activity in both univariate and multivariate analysis **(table 7).**

Table 3. Laboratory data of the study groups

Parameter		jSLE group N=50	Control group N=50	P value
Hemoglobin (g/dl)	**Mean±SD**	10.3±1	11.8±0.5	<0.001*
	Range	7.6-11.8	11.1-12.6	
Hematocrit (%)	**Mean±SD**	33.7±2.8	38.6±2.7	<0.001*
	Range	25.6-36.5	33.4-44	
Red blood cells (x 10^6/cmm)	**Mean±SD**	3.9±0.8	5.1±0.6	<0.001*
	Range	3.4-4.6	4.3-5.6	
MCH (pg)	**Mean±SD**	23.5±3.4	28.6±3.1	<0.001*
	Range	21-28	27-31	
MCV (fl)	**Mean±SD**	61.9±2.2	73.4±2.4	<0.001*
	Range	57.5-67.9	61.8-77.4	
RDW (%)	**Mean±SD**	15.8±0.8	12.8±1.4	<0.001*
	Range	14.2-17.4	10.3-15.1	
TLC (x10^3/cmm)	**Mean±SD**	8.4±2.2	8.6±2.6	0.71
	Range	3.2-12.4	4.1-11.6	
Neutrophils (x10^3/cmm)	**Mean±SD**	6.2±1.8	4.6±1.6	<0.001*
	Range	2.1-11.3	2.5-8.5	
Lymphocytes (x10^3/cmm)	**Mean±SD**	2.3±0.8	3.8±1.3	<0.001*
	Range	0.7-4.2	1.3-6	
Platelets (x10^3/cmm)	**Mean±SD**	233.6±76.3	303.1±58.2	<0.001*
	Range	85-333	176-420	
AST (U/L)	**Mean±SD**	46.9±15.6	10.3±3.6	<0.001*
	Range	17-70	7-22	
ALT (U/L)	**Mean±SD**	43.1±20.8	17.7±3.7	0.001*
	Range	18-82	8-22	
Urea (mg/dL)	**Mean±SD**	53.1±16.2	16.9±6.1	<0.001*
	Range	12-84	9-30	
Creatinine (mg/dL)	**Mean±SD**	1.2±0.33	0.59±0.2	0.005*
	Range	0.45-1.74	0.2-1	
CRP (mg/L)	**Mean±SD**	22.7±11.5	4.1±1.8	<0.001*
	Range	6-96	1-6	
ESR (mm/hr)	**Mean±SD**	61±24.9	12.6±3.9	<0.001*
	Range	22-107	6-20	
NLR	**Mean±SD**	3.1±1.5	1.3±0.3	<0.001*
	Range	1.1-7.1	0.8-2.1	
PLR	**Mean±SD**	109.4±37.4	81.7±30.6	<0.001*
	Range	50.7-196	33.2-142.9	
RPR	**Mean±SD**	0.08±0.04	0.046±0.03	<0.001*
	Range	0.05-0.20	0.03-0.07	

jSLE: Juvenile systemic lupus erythematosus; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; RDW: Red cell distribution width; TLC: Total leucocyte count; AST: Aspartate aminotransferase; ALT: Alanine Aminotransferase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; RPR: Red cell distribution width/ platelet ratio.

Table 4. The correlation between hematological parameters and disease-related parameters

Parameters		RDW (%)	NLR	PLR	RPR
Age (years)	**r**	-0.113	0.145	-0.159	-0.032
	P value	0.485	0.201	0.270	0.844
Disease duration (years)	**r**	0.288	0.249	0.321	0.298
	P value	**0.011***	**0.021***	**0.001***	**0.014***
AST (U/L)	**r**	-0.024	-0.115	-0.143	-0.058
	P value	0.786	0.231	0.121	0.324
ALT (U/L)	**r**	0.104	0.144	0.092	0.106
	P value	0.213	0.243	0.254	0.276
Urea (mg/dL)	**r**	0.122	0.188	0.140	0.130
	P value	0.211	0.176	0.189	0.193
Creatinine (mg/dL)	**r**	0.048	-0.066	-0.046	-0.128
	P value	0.856	0.765	0.675	0.132
Hemoglobin (g/dl)	**r**	-0.678	-0.618	-0.279	-0.355
	P value	**<0.001***	**<0.001***	**<0.001***	**<0.001***
TLC (x10^3/cmm)	**r**	-0.125	0.178	-0.259	-0.089
	P value	0.385	0.216	0.070	0.539
Neutrophils (x10^3/cmm)	**r**	0.188	0.202	-0.084	0.021
	P value	0.191	0.061	.562	.885
Lymphocytes (x10^3/cmm)	**r**	-0.464	-0.715	-0.443	-0.458
	P value	**<0.001***	**<0.001***	**<0.001***	**<0.001***
CRP (mg/L)	**r**	0.454	0.544	0.492	0.206
	P value	**<0.001***	**<0.001***	**<0.001***	**0.040***
ESR (mm/hr)	**r**	0.622	0.588	0.440	0.330
	P value	**<0.001***	**<0.001***	**<0.001***	**0.001***
C3 (g/L)	**r**	0.048	-0.366	-0.346	-0.228
	P value	0.739	**0.012***	**0.014***	0.079
C4 (g/L)	**r**	-0.255	-0.371	-0.357	0.280
	P value	0.074	**0.009***	**0.013***	0.059
SLEDAI-2k	**r**	0.206	0.788	0.326	0.368
	P value	0.152	**<0.001***	**0.021***	**0.008***
SDI score	**r**	0.061	0.530	0.370	0.366
	P value	0.672	**<0.001***	**0.011***	**<0.001***

RDW: Red cell distribution width; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; RPR: Red cell distribution width/ platelet ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TLC: Total leucocyte count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; C3: Complement 3; C4: Complement 4; SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000; SDI score: The SLICC/ACR Damage Index.

Table 5. The association of hematological parameters with jSLE disease activity by SLEDAI-2K and by serological parameters

		Activity by SLEDAI-2k			Serological activity		
	Parameter	**Active**	**Inactive**	**p-value**	**Active**	**Inactive**	**p-value**
		N=22	**N=28**		**N=35**	**N=15**	
RDW (%)	**Mean±SD**	15.9±0.9	15.6±1.3	0.52	15.9±1.4	15.2±0.96	0.08
	Range	14.5-17.7	14.2-17.5		14.2-17.7	14.4-17.1	
NLR	**Mean±SD**	4.1±1.4	2.3±0.9	**0.001***	4.9±1.3	2.3±0.8	**<0.001***
	Range	1.9-7.1	1.1-4.2		2.1-7.1	1.1-4.2	
PLR	**Mean±SD**	126.2±38.2	96.1±33.2	**0.005***	136.5±32.4	91.3±39.1	**<0.001***
	Range	80.9-196	50.7-145.3		100.9-196	50.7-141.1	
RPR	**Mean±SD**	0.11±0.09	0.07±0.03	**0.019***	0.12±0.07	0.07±0.03	**<0.001***
	Range	0.07-0.20	0.05-0.09		0.07-0.20	0.05-0.10	

SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000; RDW: Red cell distribution width; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; RPR: Red cell distribution width/platelet ratio.

Table 6. Diagnostic performance of hematological parameters to detect disease activity by ROC curve analysis

Hematological parameters	**AUC**	**95% CI**		**Cut-off value**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**PLR**	**NLR**	**P value**
NLR	0.850	0.743	0.957	2.9	86.4%	89.6%	89.1%	91.2%	8.3	0.15	<0.001*
PLR	0.729	0.586	0.871	125	68.1%	83.1%	78.8%	79.4%	4	0.38	0.006*
RPR	0.636	0.476	0.795	0.06	63.6%	56.3%	77.9%	72.3%	1.4	0.65	0.013*
RDW	0.516	0.352	0.681	15.6	50%	35.7%	45.6%	50.3%	0.8	1.4	0.845

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; RPR: Red cell distribution width/platelet ratio; RDW: Red cell distribution width; AUC: Area under the curve; 95% CI: 95% confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

Table 7. Univariate and multivariate regression analysis of predictors of disease activity

Parameter	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Hemoglobin	0.711	0.561-0.971	<0.001*	0.770	0.561-1	0.073
Neutrophils	1.211	0.989-1.523	0.152			
Lymphocytes	0.776	0.523-0.934	<0.001*	0.786	0.554-0.997	<0.001*
Platelets	0.892	0.712-1.188	0.076			
RDW (%)	1.279	0.734-3.090	0.257			
CRP	1.101	0.718-1.308	0.213			
C3	0.889	0.732-0.982	0.322			
C4	0.934	0.812-0.976	0.398			
ESR	1.772	1.101-2.910	<0.001*	1.790	1.221-2.890	0.002*
NLR	1.360	1.103-1.954	<0.001*	1.801	1.333-2.223	<0.001*
PLR	1.354	1.103-1.876	<0.001*	1.784	1.244-2.054	0.004*
RPR	2.043	1.432-2.654	<0.001*	1.967	1.658-2.844	<0.001*

RDW: Red cell distribution width; CRP: C-reactive protein; C3: Complement 3; C4: Complement 4; ESR: Erythrocyte sedimentation rate; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; RPR: Red cell distribution width/platelet ratio, OR: Odds ratio.

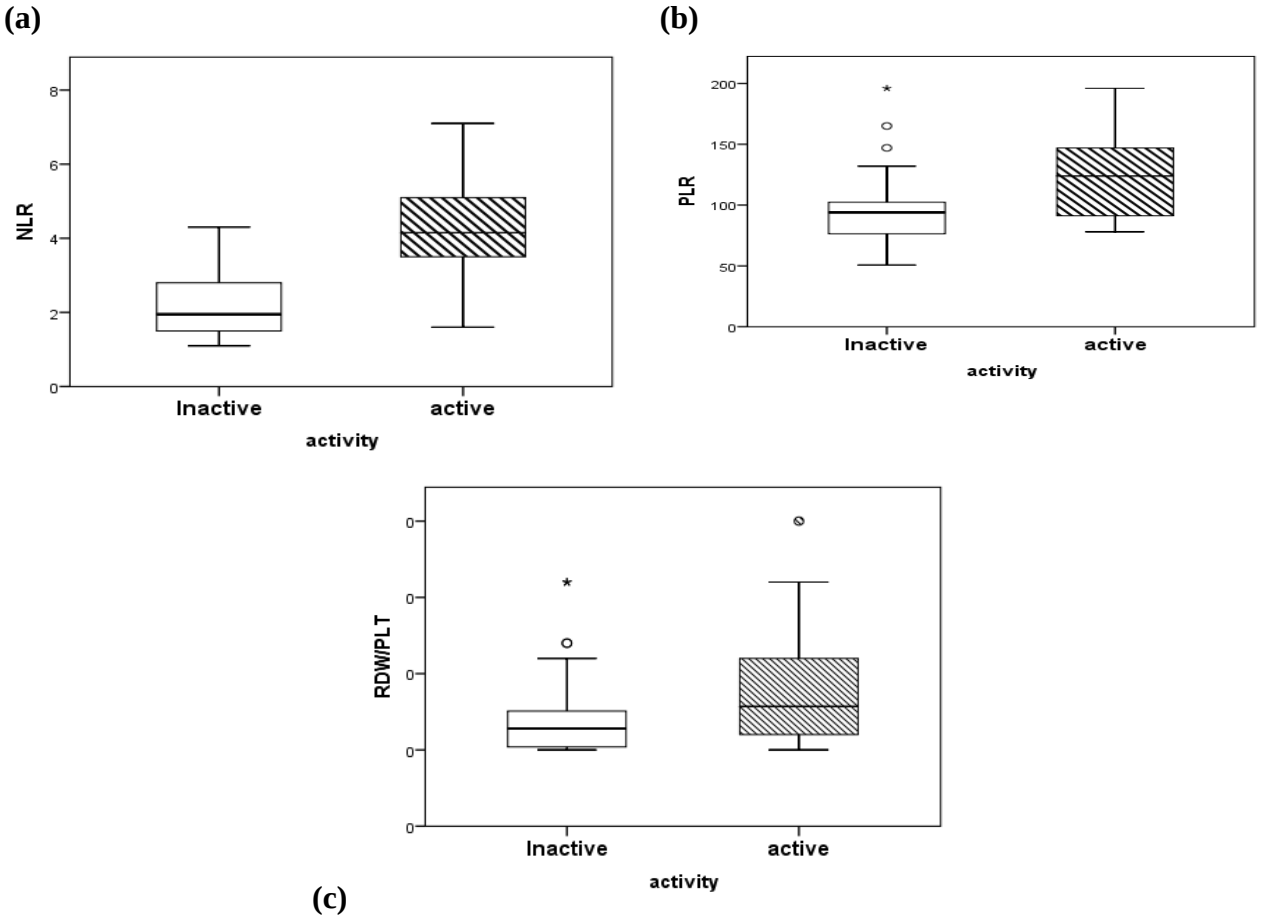

Figure 2: (a) NLR (b) PLR (C) RPR in patients with active and inactive state by SLEDAI-2k

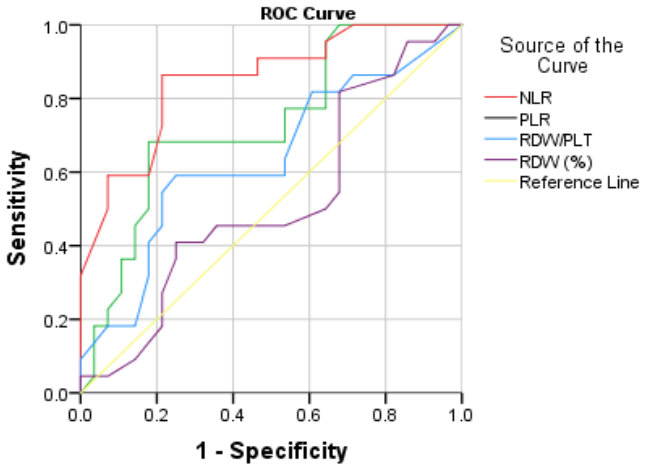

Figure 3: ROC curve of performance of hematological parameters to detect disease activity

Discussion

This case control study involved fifty jSLE patients and a matching healthy control to demonstrate the importance of hematological parameters in assessing jSLE disease activity. It was found that NLR, PLR, and RPR were substantially raised in jSLE patients and were considerably associated with disease activity.

It is commonly known that variations in the number of circulating white blood cells, particularly in relation to lymphocytes and neutrophils, are indicative of systemic inflammation. [22] Compared to separate neutrophils, lymphocytes, and total white blood cells, NLR and PLR are less susceptible to a variety of physiological and pathological circumstances. As a result, NLR and PLR may be new indicators for inflammation. [14]

In the current study, hematological parameters, namely RDW, NLR, PLR, and RPR were substantially elevated in patients than controls and positively correlated with duration of disease, markers of disease activity as CRP, ESR, SLEDAI-2k and SDI scores, and negatively correlated with hemoglobin. Additionally, NLR and PLR were negatively correlated with complement levels. Moreover, patients having active state had statistically higher NLR, PLR and RPR than patients with inactive state, while there was no statistical difference as regards to RDW.

These hematological parameters were frequently utilized to assess the clinical inflammatory progression of both autoimmune and non-autoimmune illnesses, due to the fact that they are inexpensive, simple to compute, and rarely affected by physiological, pathological, or physical conditions. [23]

Numerous earlier studies have examined NLR in SLE. Accordingly, it has been demonstrated that NLR is higher in SLE groups than in healthy controls and is correlated with disease activity, [11-13] NLR was correlated positively with SLEDAI-2k index of disease activity, [24, 25] and with markers of disease activity as ESR and CRP, but this correlation was not detected with complement level. [25]

In another study, NLR showed negative correlation with hemoglobin and complement level. [13] Furthermore, it has been demonstrated that NLR dramatically drops following therapy. [24]

Platelet/lymphocyte ratio, like NLR, is another inflammatory marker commonly utilized in routine blood testing. In previous studies, PLR was similarly investigated, it was demonstrated that SLE patients have higher PLR compared to controls. [26, 27] PLR was linked to the

duration of disease and showed a substantial rise among active disease patients as determined by the SLEDAI-2k, suggesting that PLR is a useful indicator in the management of SLE illness. [13, 14]

Furthermore, when SLE patients were compared to those with other rheumatic inflammatory disorders, their PLR was noticeably greater, thus, PLR may be a significant marker to diagnose SLE. [28]

PLR was linked with several of the parameters under study, including a positive correlation with ESR and CRP and an inverse correlation with C3, with a highly significance degree than NLR. According to these findings, PLR is a better indicator of the severity of SLE disease than NLR. Additionally, there was a positive association between NLR and PLR. [29]

In another investigation, the PLR showed a strong correlation with disease activity and was able to predict it; however, the damage index did not show any correlation with PLR [28]. In a subsequent study, PLR was linked to the disease duration, had a negative correlation with hemoglobin and complement levels, and considerably increased in patients with active disease as determined by SLEDAI-2k [13]. While platelet and lymphocyte counts typically decline in SLE patients, PLR only varies in response to shifts in disease activity. [30]

In a previous meta-analysis, NLR and PLR were reported to be significantly greater in SLE patients, and they also showed a positive correlation with SLEDAI-2k. This shows that NLR and PLR may be helpful markers in the treatment of SLE. [14]

However, aanother investigation indicated that SLE patients had considerably increased NLR and PLR, but they were unable to identify any correlation with disease activity. This may be because most of the individuals had mild to moderate disease activity. [31]

According to a different study on jSLE, NLR and PLR correlated with serological markers and might be used to expect organ involvement in jSLE, specifically cutaneous, arthritis, serositis, and haematological involvement. [12]

Since NLR and PLR are complementary, it has been preferred to determine them together in inflammatory rheumatic illnesses. NLR determination, which mostly shows the existence of leukocyte inflammation, problems from different infections, and serious organ damage in SLE, can help more efficiently with disease activity monitoring. Especially in individuals with multisystem involvement, PLR is believed to be significant in assessing the level of systemic inflammation and in predicting infections and other concomitant diseases, its value reflects variations in inflammation and cytokine levels. [30, 31] These findings highlight the fact that lymphopenia are more important in SLE physiopathology than thrombocytopenia or neutropenia. [32]

In this study, RDW was increased in jSLE patients than controls, This is consistent with earlier research that found that individuals with SLE had higher RDW. The influence of inflammatory cytokines causes premature erythrocytes to be released into the bloodstream, which in turn causes an increase in RDW. [33] In a prior study, regardless of anemia status, RDW was higher among patients than controls, demonstrating the impact of SLE on red blood cells. Therefore, RDW was linked to serological activity and inflammatory indicators like CRP, fibrinogen, or D-dimer, and the SLEDAI-2K as well. This result confirms that RDW is a sign of tissue injury and persistent inflammation. [13]

On the other hand, our results didn't show a significant change in RDW between patients with active and with inactive disease, this also matched a previous study that reported no substantial variation of RDW between nonactive-SLE and active-SLE ($p = 0.27$). [34]

In contrast, a previous report found that RDW differentiated between inactive SLE and low disease activity patients and between low and high disease activity. [35]

The RPR, a combination of two independent parameters, has been recognized as a novel indicator reflecting the inflammatory degree. [36] In this study, RPR was associated with jSLE patients and was linked to disease activity. Similarly, it was reported that RPR level was correlated with clinical SLE activity and its value returned to normal following treatment [37] therefore, RPR was substantially linked with SLE disease activity. [38]

In agreement with our study, it was observed previously that SLE patients had a substantially decreased mean platelets compared to control group. SLE patients had a considerably greater RDW value compared to controls. SLE patients had a substantially greater RPR than controls, p=0.01. [38] Furthermore, active SLE patients were exposed to significantly rising NLR and PLR than inactive disease patients. While the RDW values between the active and inactive groups did not significantly change. [39]

In the present study, on assessment of the value of hematological parameters as indicators of disease activity by ROC curve; NLR revealed the highest AUC (0.850), with the highest sensitivity (86.4%), and specificity (89.6%), at a cut-off value 2.9, followed by PLR with AUC (0.729), with a sensitivity (68.1%), and specificity (83.1%), at a cut-off value 125, then RPR with AUC (0.636) with a sensitivity (63.6%) and specificity (77.9%), at a cut-off value (0.06).

Likewise, in another study, NLR and PLR diagnostic performances of SLE disease activity by SLEDAI-2k were identical, with AUC 0.64 (p = 0.003) and 0.65 (p = 0.003), and cutoff points of 1.64 and 114.76, respectively. [29] In a third study, the AUC for PLR was greater than that of NLR and RDW (0.71, 0.63 and 0.53, respectively). [39]

In the current study, using logistic regression analysis, low hemoglobin level, low lymphocyte count, high ESR, NLR, PLR and RPR were significant predictors of disease activity by univariate analysis, and they remained significant in the multivariate analysis except hemoglobin level.

Similarly, in another study, ESR, CRP, NLR, PLR, C3, anti-dsDNA, anti-nucleosome, anti-C1q antibodies, and serum and urinary MCP-1 shown to be independent predictors of disease activity by univariate analysis, $p < 0.001$, suggesting that NLR and PLR, two commonly available and affordable hematological markers, can be used to assess disease activity in standard clinical practice. Multivariate regression displayed ESR and serum MCP-1 as the main predictors of disease activity in SLE. [29]

Finally, because the study was made at a single center and the sample size was small, there are some underlying limitations. The study's cross-sectional methodology prevented it from reflecting the relationship over time, and it did not examine how treatment affected hematological markers. Furthermore, erroneous judgments could result from the disease's diversity and complexity. Therefore, additional prospective research is needed to evaluate the cutoff values and validate these findings.

Conclusion

The current study of jSLE revealed that RDW, NLR, PLR, and RPR were higher in jSLE patients than controls. Patients with active disease state had considerably higher NLR, PLR and RPR compared to patients with inactive state. Lymphocytes, ESR, NLR, PLR and RPR were independent predictors of SLE disease activity. Therefore, NLR, PLR, and RPR can serve as a simple, inexpensive, and easily accessible biomarker for indicating jSLE disease activity.

Conflict of interest

No conflict of interest to declare by the contributors.

References

1. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis., 2021; 80(1):14-25.
2. Fayyaz A, Igoe A, Kurien BT, Danda D, James JA, Stafford HA, Scofield RH. Haematological Manifestations of Lupus, Lupus Sci. Med. 2015;2:e000078.
3. Ameer MA, Chaudhry H, Mushtaq J, Khan OS, Babar M, Hashim T, et al. An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022;14.
4. Wen L, Chen Z, Jin Z, Pan W, Liu L, Wu M, et al. Clinical and laboratorial outcome of different age-onset systemic lupus erythematosus patients in Jiangsu, China: a multicentre retrospective study, Sci Rep. 2022;12:10683.
5. Gaitonde S, Samols D, Kushner I. C-Reactive Protein and Systemic Lupus Erythematosus. Arthritis Rheum. 2008; 59: 1814–1820.
6. Dossybayeva K, Bexeitov Y, Mukusheva Z, Almukhamedova Z, Assylbekova M, Abdukhakimova D, et al. Analysis of Peripheral Blood Basophils in Pediatric Systemic Lupus Erythematosus, Diagnostics. 2022;12:1701.
7. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, Weinrauch Y, Zychlinsky A. Neutrophil extracellular traps kill bacteria, Science. 2004;303 (5663): 1532-5.
8. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to lymphocyte ratio: an emerging marker of the relationships between the immune system and diseases, Int J Mol Sci. 2022; 23:3636.
9. Suszek D, Gorak A, Majdan M. Differential approach to peripheral blood cell ratios in patients with systemic lupus erythematosus and various manifestations, Rheumatol Int.2020; 40(10):1625–1629.
10. Soliman WM, Sherif NM, Ghanima IM, El-Badawy MA. Neutrophil to lymphocyte and platelet to lymphocyte ratios in systemic lupus erythematosus: Relation with disease activity and lupus nephritis, Reumatol Clin (Engl Ed)2020;16(4):255-261.
11. Abdalhadi S, Khalayli N, Al-Ghotani B, Kudsi M. Systemic lupus erythematosus disease activity and neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: a cross-sectional case–control study, Ann Med Surg. 2023;85:1448–53.
12. Li W, Liu S, Chen C, Han Y. Neutrophil-to-lymphocyte ratios and platelet-to-lymphocyte ratios in juvenile systemic lupus erythematosus: correlation with disease manifestations, Ann Palliat Med.2021; 10: 9406414–9414.
13. Moreno-Torres V, Castejón R, Mellor-Pita S, utor-Ureta TP, Campo PD, Martínez-Urbistondo M, et al. Usefulness of the hemogram as a measure of clinical and serological activity in systemic lupus erythematosus, Journal of Translational Autoimmunity, 2022;5:100157.
14. Ma L, Zeng A, Chen B, Chen Y, Zhou R. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with systemic lupus erythematosus and their correlation with activity: A meta-analysis, Int Immunopharmacol.2019;76 :105949.
15. Peirovy A, Mahdavi AM, Khabbazi A, Hajialilo M, Sakhinia E, Rashtchizadeh N. Clinical usefulness of hematologic indices as predictive parameters for systemic lupus erythematosus. Lab Med.2020; 51:519–28.
16. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum.1997; 40:1725.
17. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum. 2012; 64(8):2677-86.
18. Gladman DD, Ibanez D, Urowltz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J. Rheumatol. 2002;29: 288–291.
19. Shamim R, Farman S, Batool S, Khan SEA, Raja MKH. Association of systemic lupus erythematosus disease activity index score with clinical and laboratory parameters in pediatric onset systemic lupus erythematosus. Pakistan J Med Sci. 2020; 36:467.
20. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum*. 1996;39(3):363-369. doi:10.1002/art.1780390303
21. Parker B, Bruce IN. Clinical markers,

metrics, indices, and clinical trials. Dubois' Lupus Erythematosus and Related Syndromes, Ninth Edit.2018; 4.
22. Delgado LM, Estudio de la respuesta inmune periférica en la enfermedad de Parkinson (2023).
23. John-Olabode SO,Okunade KS, Olorunfemi G, Soibi-Harry A, Rimi G, Osunwusi B, et al. Pretreatment neutrophil-to-lymphocyte ratio: a prognostic biomarker of survival in patients with epithelial ovarian cancer, Cureus.2021; 13.
24. Han Q, Liang P, Li J, Liu B, Zhang R, Xie X, et al. The Ratio of Neutrophil to Lymphocyte as a Potential Marker of Clinicopathological Activity for Lupus Nephritis, Int. Urol. Nephrol.**2023**.
25. Yu H, Jiang L, Yao L, Gan C, Han X, Liu R, et al. Predictive Value of the Neutrophil-to-Lymphocyte Ratio and Hemoglobin In systemic Lupus Erythematosus. Exp. Ther. Med. 2018;16:1547–1553.
26. Li L, Xia Y, Chen C, Cheng P, Peng C. Neutrophil-lymphocyte ratio in systemic lupus erythematosus disease: a retrospective study, Int J Clin Exp Med.2015; 8:11026.
27. Wu Y, Chen Y, Yang X, Chen L, Yang Y. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with disease activity in patients with systemic lupus erythematosus, Int Immunopharmacol.2016; 36:94–9.
28. El-Said NY, El Adle S, Fathi HM. Clinical significance of platelet-lymphocyte ratio in systemic lupus erythematosus patients: Relation to disease activity and damage, The Egyptian Rheumatologist. 2022;44 (3):225-229.
29. Živković V, Cvetković T, Dinić BR, Jurišić V. Correlation of hematological parameters, antibodies and cytokines with disease activity in systemic lupus erythematosus: a cross-sectional study, Egypt Rheumatol Rehabil.2023;50:55.
30. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases, Ann Lab Med.2019; 39:345.
31. Mercader-Salvans J, García-González M, Quevedo-Abeledo JC, Quevedo-Rodríguez A, Romo-Cordero A, Ojeda-Bruno S, et al. Blood Composite Scores in Patients with Systemic Lupus Erythematosus, *Biomedicines*.2023; 11(10): 2782.
32. Sarbu MI, Salman-Monte TC, Mu˜noz PR, Lisbona MP, Bernab´e MA, Carbonell J. Differences between clinical and laboratory findings in patients with recent diagnosis of SLE according to the positivity of anti-dsDNA by the Crithidia luciliae method, Lupus.2015' 24 (11):1198–1203.
33. Mohamed OSD, Azmy GJ, Elfadl EMA. Clinical significance of red blood cell distribution width in systemic lupus erythematosus patients. Egypt Rheumatol Rehabil.2020; 47:1–8.
34. Zou XL, Lin XJ, Ni X, Wang J, Liu W, Wei J. Baseline Red Blood Cell Distribution Width Correlates with Disease Activity and Therapeutic Outcomes in Patients with Systemic Lupus Erythematosus, Irrespective of Anemia Status, Clin Lab.2016; 62: 1841–50.
35. Taha SI, Samaan SF, Ibrahim RA, Moustafa NM, El-Sehsah EM, Youssef MK. Can complete blood count picture tell us more about the activity of rheumatological diseases? Clin Med Insights Arthritis Musculoskelet Disord.2022; 15:11795441221089182.
36. Yao H, Lian L, Zheng R, Chen C. Red blood cell distribution width/platelet ratio on admission as a predictor for in-hospital mortality in patients with acute myocardial infarction: a retrospective analysis from MIMIC-IV Database, BMC Anesthesiol.2023; 23:113.
37. Xie S, Chen X. Red blood cell distribution width-to-platelet ratio as a disease activity-associated factor in systemic lupus erythematosus. Medicine (Baltimore).2018; 97: e12342.
38. Gorial FI, Ali HO, Naema SJ, Hussain SA. Association between red cell distribution width to platelet ratio and disease activity among iraqi patients with systemic lupus erythematosus, Al-Rafidain J Med Sci. 1:118–23.

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